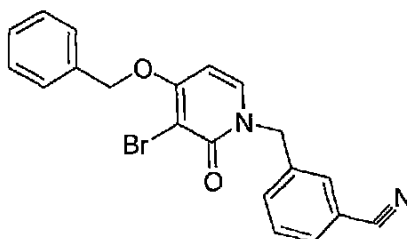


Preparation of 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile. 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (1.0 g, 3.6 mmol) was dissolved in *N,N*-dimethylformamide (5 mL). α -Bromo-*p*-tolunitrile (0.85g, 4.3 mmol) was added followed by K_2CO_3 (0.59 g, 4.3 mmol). The resulting mixture was heated to 80 °C for 16 h. The reaction was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate (3 x 100 ml). The organic extracts were combined, washed with brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (0.65 g, 46%). 1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 2H), 7.41-7.31 (m, 7H), 7.23 (d, J = 7.6 Hz, 1H), 6.11 (d, J = 8.0 Hz, 1H), 5.24 (s, 2H), 5.18 (s, 2H). ES HRMS m/z 395.0404 ($M+H$ $C_{20}H_{15}BrN_2O_2$ requires 395.0390).

Example 135

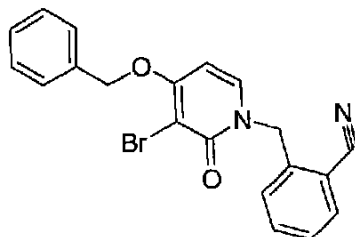
3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as described in example 134. 1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.54 (m, 3H), 7.45 (d, J = 7.6 Hz, 1H), 7.43-7.31 (m, 5H), 7.26 (d, J = 1.6 Hz, 1H), 6.12 (d, J = 1.6 Hz, 1H), 5.24 (s, 2H), 5.15 (s, 2H). ES HRMS m/z 395.0420 ($M+H$ $C_{20}H_{15}BrN_2O_2$ requires 395.0390).

Example 136

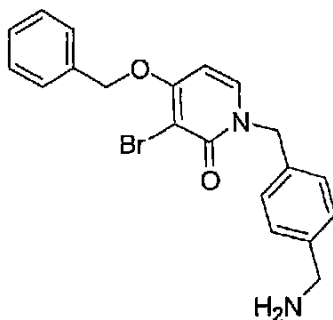
2 - { [4 - (benzyloxy) - 3 - bromo - 2 - oxopyridin - 1 (2H) -
yl] methyl } benzonitrile



The title compound was prepared by a procedure essentially as described in example 134. ^1H NMR (400 MHz, CDCl_3) δ 7.74 (d, J = 8.4 Hz, 1H); 7.63 (dd, J = 1.2, 8.0 Hz, 1H), 7.57 (dt, J = 1.2, 8.4 Hz, 1H), 7.55 (d, J = 8.0 Hz, 1H); 7.43-7.30 (m, 6H), 6.13 (d, J = 8.0 Hz, 1H), 5.33 (s, 2H), 5.23 (s, 2H). ES HRMS m/z 395.0398 ($M+H$ $\text{C}_{20}\text{H}_{15}\text{BrN}_2\text{O}_2$ requires 395.0390).

Example 137

1 - [4 - (aminomethyl) benzyl] - 4 - (benzyloxy) - 3 - bromopyridin - 2 (1H) -
one

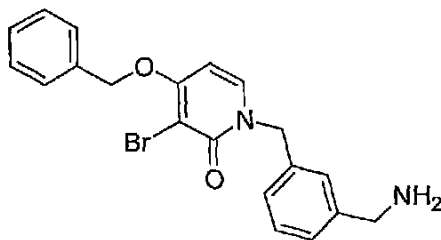


Preparation of 1 - [4 - (aminomethyl) benzyl] - 4 - (benzyloxy) - 3 - bromopyridin - 2 (1H) - one. EXAMPLE 134 (100 mg, 0.25 mmol) was dissolved in tetrahydrofuran (2 mL) under N_2 . Borane

dimethylsulfide complex (0.25 mL, 0.5mmol, 2M in tetrahydrofuran) was added. The reaction was then heated to 70°C and shaken overnight. The mixture was cooled and all the solvent was distilled under vacuum. The resulting residue
5 was partitioned between ethyl acetate and 0.2 N NaOH, and extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated to an oil, and trituated with dichloromethane and hexane to give an off-
10 white solid. (80 mg, 80%). ¹H NMR (400 MHz, d₆DMSO) δ 7.90 (d, *J* = 7.6 Hz, 1H); 7.43-7.21 (m, 9H), 6.70 (d, *J*=7.6 Hz, 1H), 5.29 (s, 2H), 5.08 (s, 2H), 3.71 (s, 2H). ES HRMS *m/z* 399.0721 (M+H C₂₀H₁₉BrN₂O₂ requires 399.0703).

15 Example 138

1- [3- (aminomethyl)benzyl] -4- (benzyloxy) -3-bromopyridin-2 (1H) -
one

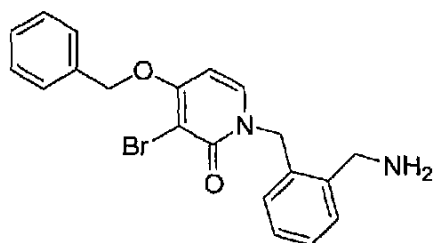


20

The title compound was prepared by a procedure essentially as described in Example 137 using the title compound of Example 135 as starting material. ¹H NMR (400 MHz, d₆DMSO) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.44-7.22 (m, 9H), 6.50 (d, *J*=7.6 Hz, 1H),
25 5.30 (s, 2H), 5.12 (s, 2H), 3.88 (s, 2H). ES HRMS *m/z* 399.0730 (M+H C₂₀H₁₉BrN₂O₂ requires 399.0703).

Example 139

1- [2- (aminomethyl)benzyl] -4- (benzyloxy) -3-bromopyridin-2 (1H) -
one



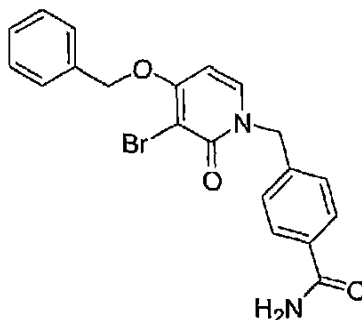
5

The title compound was prepared by a procedure essentially as described in Example 137 using the title compound of Example 136 as starting material. ¹H NMR (400 MHz, d₆DMSO) δ 7.88 (d, J = 8.0 Hz, 1H); 7.45-7.34 (m, 5H), 7.26- 7.21 (m, 3H); 6.85 (d, J=7.2 Hz, 1H), 6.53 (d, J=7.6 Hz, 1H), 5.32 (s, 2H), 5.12 (s, 2H), 3.90 (s, 2H). ES HRMS m/z 399.0699 (M+H C₂₀H₁₉BrN₂O₂ requires 399.0703).

Example 140

15

4- { [4- (benzyloxy) -3-bromo-2-oxopyridin-1 (2H) -
yl]methyl}benzamide

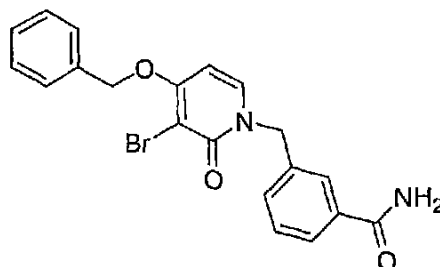


20 Preparation of 4- { [4- (benzyloxy) -3-bromo-2-oxopyridin-1 (2H) -yl]methyl}benzamide. EXAMPLE 134 (100 mg, 0.25 mmol) was added to a suspension of potassium fluoride (40% on alumina) in t-butyl alcohol, heated to 85°C, and stirred for 20h. The

alumina was removed by filtration and washed with dichloromethane and water. The resulting filtrate was separated and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The organic extracts were
 5 combined, dried over Na₂SO₄, and filtered. The filtrate was concentrated to an oil. Trituration with dichloromethane and hexane gave a solid (11.5 mg, 11%). ¹H NMR (400 MHz, d₆DMSO) δ 7.94 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H); 7.43-7.29 (m, 7H), 6.51 (d, J=7.6 Hz, 1H), 5.31 (s, 2H), 5.16 (s, 2H).
 10 ES HRMS m/z 413.0541 (M+H C₂₀H₁₇BrN₂O₃ requires 413.0495).

Example 141

3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-
 yl]methyl}benzamide



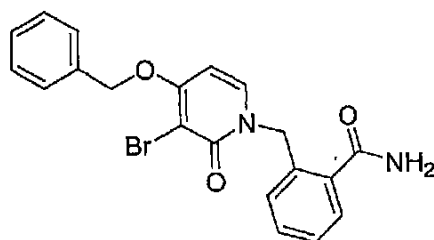
15

The title compound was prepared by a procedure essentially as described in Example 140 using the title compound of Example 135 as starting material. ¹H NMR (400 MHz, d₆DMSO) δ 7.95 (d, J = 7.6 Hz, 2H), 7.76 (m, 2H); 7.43-7.26 (m, 8H), 6.51 (d, J=7.6 Hz, 1H), 5.31 (s, 2H), 5.15 (s, 2H).
 20 ESHRMS m/z 413.0497 (M+H C₂₀H₁₇BrN₂O₃ requires 413.0495).

Example 142

2-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-
 yl]methyl}benzamide

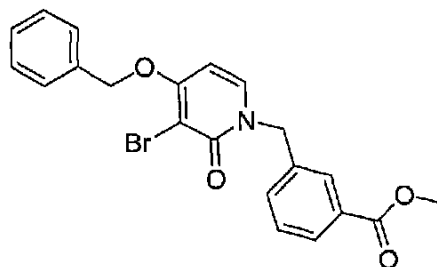
25



The title compound was prepared by a procedure essentially as described in Example 140 using the title compound of Example 136 as starting material. ¹H NMR (400 MHz, d₆DMSO) δ 7.78 (d, J = 7.6 Hz, 1H), 7.54 (dd, J = 1.6, 7.6 Hz, 1H); 7.45 (d, J=7.6 Hz, 2H); 7.44-7.32 (m, 5H), 7.15 (d, J=7.6 Hz, 1H), 6.49 (d, J=7.6 Hz, 1H), 5.39 (s, 2H), 5.30 (s, 2H). ES HRMS m/z 4413.0506 (M+H C₂₀H₁₇BrN₂O₃ requires 413.0495).

10 Example 143

Methyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate



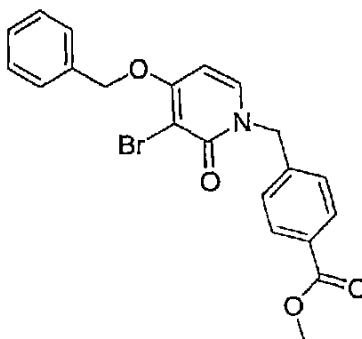
15

Preparation of Methyl 3-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate. EXAMPLE 134 (100 mg, 0.25 mmol) was suspended in methanol and cooled to 0°C. HCl (g) was bubbled through the mixture until saturated (~30 minutes). The reaction was warmed to ambient temperature and stirred for 4 hours. HCl and methanol were removed in vacuo, yielding an oil, that was purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (3 mg, 3%). ¹H NMR

(400 MHz, CD₃OD) δ 7.98 (app d, J = 8.0 Hz, 2H), 7.77 (app d, J = 8.0 Hz, 1H); 7.55 (app d, J = 8.0 Hz, 2H); 7.41-7.35 (m, 5H), 6.52 (d, J = 7.6 Hz, 1H), 5.31 (s, 2H), 5.27 (s, 2H); 3.88, (s, 3H). API-ES MS m/z 429.0 (M+H C₂₁H₁₈BrNO₄ requires 428.0492).

Example 144

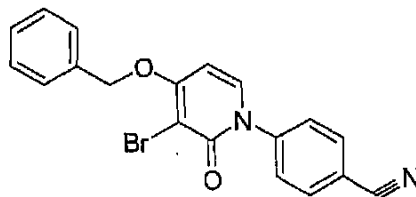
Methyl 4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}benzoate



The title compound was prepared by a procedure essentially as described in Example 143 using the title compound of Example 134 as starting material. ¹H NMR (400 MHz, CD₃OD) δ 7.94 (app d, J = 8.4 Hz, 2H), 7.76 (app d, J = 7.6 Hz, 1H); 7.46 (app d, J = 8.0 Hz, 2H); 7.39-7.35 (m, 5H), 6.51 (d, J =7.6 Hz, 1H), 5.31 (s, 2H), 5.26 (s, 2H); 3.88, (s, 3H). ES HRMS m/z 428.0492 (M+H C₂₁H₁₈BrNO₄ requires 428.0492).

Example 145

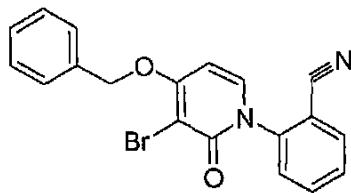
4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile



Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-
5 yl]benzonitrile 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (100 mg, 0.36 mmol) was suspended in dimethylsulfoxide (5 mL), cesium carbonate (375 mg, 1.15 mmol) was added and the reaction was shaken for 5 minutes. 4-Fluorobenzonitrile (52 mg, 0.43 mmol) was then added, the
10 reaction was heated to 80°C, and stirred. Reaction was monitored by LC/MS, and after 4h was heated to 100°C and stirred for 16 hours. Reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (5 x 50 mL). The organic extracts were combined,
15 washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (40 mg, 29%). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.44-7.42 (m, 4H),
20 7.28 (d, J = 7.6 Hz, 1H), 7.26 (s, 1H), 6.24 (d, J = 7.6 Hz, 1H); 5.31, (s, 2H). ES HRMS m/z 381.0230 (M+H C₁₉H₁₃BrN₂O₂ requires 381.0233).

Example 146

25 2-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile

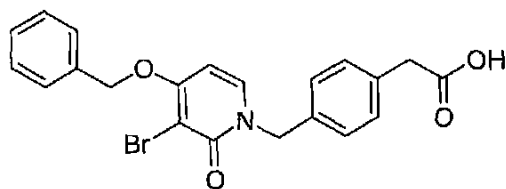


Preparation of 2-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-

5 methylpyridin-2(1H)-one (100 mg, 0.36 mmol) was suspended in dimethylsulfoxide (5 mL), cesium carbonate (375 mg, 1.15 mmol) was added and the reaction was shaken for 5 minutes. 4-Fluorobenzonitrile (52 mg, 0.43 mmol) was then added and the reaction was heated to 80°C with stirring. Reaction was
10 monitored by LC/MS, and after 4h was heated to 100°C and stirred for 16 hours. The reaction mixture was partitioned between water and ethyl acetate and extracted with ethyl acetate (5 x 50 mL). The organic extracts were combined, washed with brine, dried over Na₂SO₄, and filtered. The
15 filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (18 mg, 13%). ¹H NMR (400 MHz, CDCl₃) δ 7.81 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.73 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.57 (dt, *J* = 0.8, 8.0 Hz, 1H), 7.50-7.36 (m, 6H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 8.0 Hz, 1H); 5.31 (s, 2H). ES HRMS *m/z*
20 381.0249 (M+H C₁₉H₁₃BrN₂O₂ requires 381.0233). Example 147

(4-{[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]methyl}phenyl)acetic acid

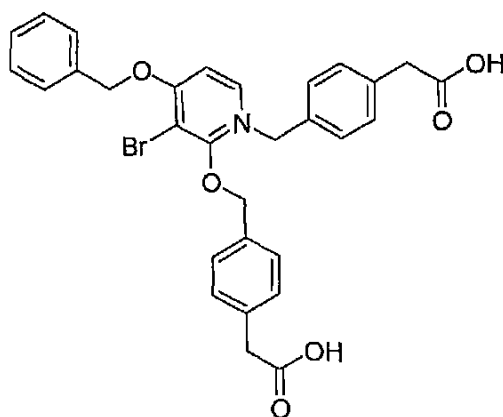
25



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-
one (0.5g, 1.78 mmol) was dissolved in *N,N*-dimethylformamide (5
mL). 4-(Bromomethyl)phenylacetic acid (0.5 g, 2.14 mmol) was
added followed by K_2CO_3 (0.3 g, 2.14 mmol). The reaction was
5 heated to 80°C and shaken for 16 hours, then heated to 100°C
and shaken for 16 hours more. The reaction mixture was
partitioned between water and ethyl acetate and extracted with
ethyl acetate (2 x 50 mL). The aqueous layer was acidified
(pH 2) with 1N HCl and extracted with ethyl acetate (3 x 50
10 mL). The organic extracts were combined, washed with brine,
dried over Na_2SO_4 , and filtered. The filtrate was concentrated
to an oil, and purified by chromatography (silica gel,
hexane/ethyl acetate) followed by reversed phase
chromatography (C_{18} , 0.1% aqueous trifluoroacetic acid
15 /acetonitrile) to yield a white solid (25 mg, 3%). 1H NMR (400
MHz, $CDCl_3$) δ 7.40-7.38 (m, 3H), 7.25-7.20 (m, 7H), 6.05 (d, J
= 8.0 Hz, 1H), 5.21 (s, 2H); 5.13, (s, 2H); 3.62, (s, 2H).
ES HRMS m/z 428.0510 ($M+H$ $C_{21}H_{18}BrNO_4$ requires 428.0492).

20 Example 148

{4-[(4-(benzyloxy)-3-bromo-2-{[4-(carboxymethyl)benzyl]oxy}-
11lambda⁵-pyridin-1-yl)methyl]phenyl}acetic acid

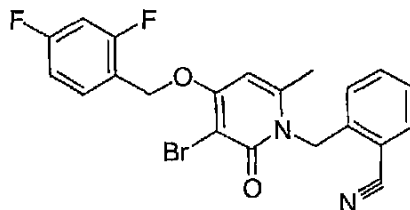


Preparation of {4-[(4-(benzyloxy)-3-bromo-2-{[4-(carboxymethyl)benzyl]oxy}-1λ⁵-pyridin-1-yl)methyl]phenyl}acetic acid. The desired product was isolated by reversed phase chromatography (C₁₈, 0.1% aqueous

5 trifluoroacetic acid/acetonitrile) using the preparation of Example 147 yielding a white solid (53 mg, 5%). ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.38 (m, 3H), 7.27-7.24 (m, 6H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.06 (d, *J* = 7.6 Hz, 1H), 5.21 (s, 2H); 5.11 (s, 2H);
10 5.11 (s, 2H); 3.63 (s, 2H); 3.58 (s, 2H). ES HRMS *m/z* 576.1009 (M+H C₃₀H₂₈BrNO₆ requires 576.1016).

Example 149

15 2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

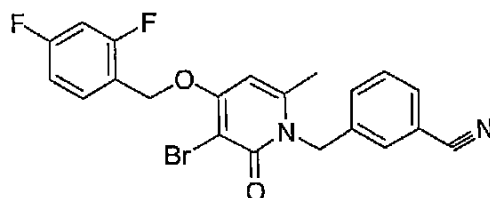


20 Preparation of 2-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile. 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (50 mg, 0.15 mmol) was dissolved in tetrahydrofuran (2 mL). α-Bromo-*o*-tolunitrile (44 mg, 0.23 mmol) was added followed by sodium
25 hydride (7.2 mg, 0.18 mmol, 60% in mineral oil) and sodium iodide (56 mg, 0.38 mmol). The reaction was heated to 50°C and stirred for 16 hours. The reaction was filtered through Celite® and the filtrate was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with

ethyl acetate (4 x 10 mL). The organic extracts were combined, washed with brine, dried over MgSO_4 , and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a
5 white solid (25 mg, 37%). ^1H NMR (400 MHz, CDCl_3) δ 7.68 (dd, J = 8.0, 1.2 Hz, 1H); 7.58 (app q, J = 8.8 Hz, 1H); 7.52 (dt, J = 8.0 & 1.2 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H); 7.08 (d, J = 8.8 Hz, 1H), 7.00-6.93 (m, 1H); 6.89-6.84 (m, 1H); 6.05 (s, 1H), 5.57 (s, 2H), 5.22 (s, 2H); 2.28, (s, 3H). ES HRMS m/z
10 445.0335 ($\text{M}+\text{H}$ $\text{C}_{21}\text{H}_{15}\text{BrF}_2\text{N}_2\text{O}_2$ requires 445.0358).

Example 150

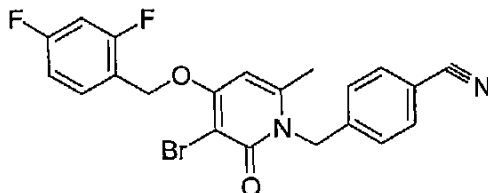
3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-
15 1(2H)-yl]methyl}benzonitrile



The title compound was prepared by a procedure essentially as
20 described in Example 149 using 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (1 g, 3.0 mmol) as starting material. ^1H NMR (CDCl_3 , 400 MHz) δ 7.61-7.55 (m, 2H); 7.45-7.41 (m, 3H); 6.98-6.94 (m, 1H); 6.89-6.84 (m, 1H); 6.03 (s, 1H), 5.36 (s, 2H), 5.22 (s, 2H); 2.30, (s, 3H). ES
25 HRMS m/z 445.0349 ($\text{M}+\text{H}$ $\text{C}_{21}\text{H}_{15}\text{BrF}_2\text{N}_2\text{O}_2$ requires 445.0358)

Example 151

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



5

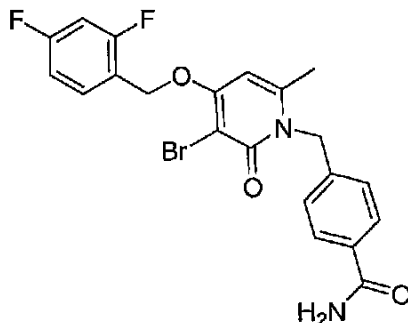
The title compound was prepared by a procedure essentially as described in Example 149 using 3-bromo-4-(2,4-difluorophenoxy)-6-methylpyridin-2(1H)-one (1 g, 3.0 mmol) as starting material. ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 8.4 Hz, 2H); 7.62-7.56 (m, 1H); 7.27 (d, *J* = 8.8 Hz, 2H); 6.95 (*app t*, *J* = 8.4 Hz, 1H), 6.88-6.83 (m, 1H); 6.03 (s, 1H), 5.39 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS *m/z* 445.0359 (*M*+H C₂₁H₁₅BrF₂N₂O₂ requires 445.0358).

15

Example 152

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide

20

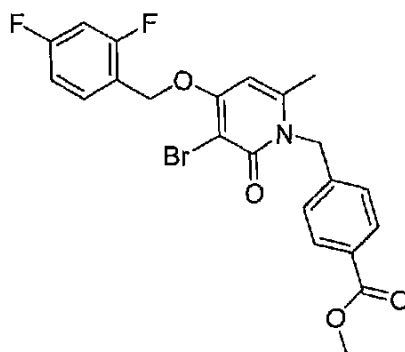


EXAMPLE 151 (50 mg, 0.11 mmol) was added to a suspension of potassium fluoride (40% on alumina) in *t*-butyl alcohol. The

reaction was heated to 90°C and stirred for 20 hours. Alumina was removed by filtration and washed with dichloromethane and water. The resulting filtrate was separated and the aqueous layer was extracted with
5 dichloromethane (2 x 20 mL). The organic extracts were combined, dried over Na₂SO₄ and filtered. The filtrate was concentrated to an oil which was purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid, yielding the product (13 mg, 25%). ¹H NMR (400 MHz, CDCl₃) δ
10 7.75 (app d, J = 8.4 Hz, 2H), 7.58 (app q, J = 8.4 Hz, 1H);
7.24 (d, J = 8.4 Hz, 2H); 6.98-6.94 (m, 1H), 6.89-6.83 (m, 1H)
6.01 (s, 1H); 5.40 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES
HRMS m/z 463.0486 (M+H C₂₁H₁₇BrF₂N₂O₃ requires 463.0463).

15 Example 153

Methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate



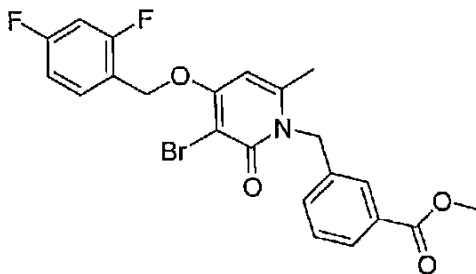
20

EXAMPLE 151 (50 mg, 0.11 mmol) was suspended in methanol and cooled to 0°C. HCl (g) was bubbled through the mixture until saturated (~30 minutes). Reaction was sealed, warmed to
25 ambient temperature, and stirred for 2 hours. HCl and methanol were removed *in vacuo*, yielding an oil, that was purified by chromatography (silica gel, hexane/ethyl acetate)

to yield a white solid (19 mg, 36%). ¹H NMR (400 MHz, CDCl₃) δ 7.97 (app d, J = 8.4 Hz, 2H), 7.58 (app q, J = 8.0 Hz, 1H); 7.22 (d, J = 8.4 Hz, 2H); 6.95 (app dt, J = 1.5, 9.6 Hz, 1H), 6.89-6.83 (m, 1H), 6.00 (s, 1H); 5.41 (s, 2H), 5.21 (s, 2H);
 5 3.90, (s, 3H); 2.27 (s, 3H). ES HRMS m/z 478.0461 (M+H C₂₂H₁₈BrNO₄ requires 478.0460).

Example 154

10 Methyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate

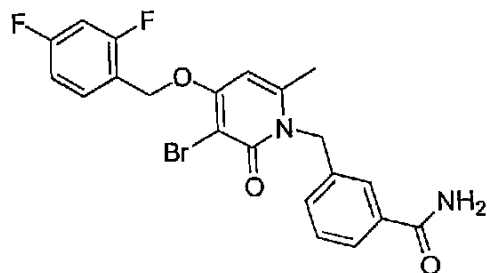


15 The title compound was prepared by a procedure essentially as described in Example 149 using the title compound of Example 150 as starting material. ¹H NMR (400 MHz, CDCl₃) δ 7.95-7.92 (m, 1H); 7.84 (bs, 1H); 7.58 (app q, J = 8.0 Hz, 1H); 7.39-7.37 (m, 2H); 6.95 (app dt, J = 1.6, 8.4 Hz, 1H), 6.88-6.83
 20 (m, 1H), 6.00 (s, 1H); 5.40 (s, 2H), 5.21 (s, 2H); 3.90, (s, 3H); 2.30 (s, 3H). ES HRMS m/z 478.0449 (M+H C₂₂H₁₈BrNO₄ requires 478.0460).

Example 155

25

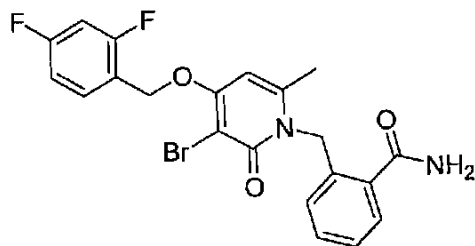
3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide



The title compound was prepared by a procedure essentially as described in Example 152 using the title compound of Example
 5 150 as starting material. ^1H NMR (400 MHz, CDCl_3) δ 7.68-7.66 (m, 2H), 7.57 (app q, $J = 8.4$ Hz, 1H); 7.42-7.34 (m, 2H); 6.98-6.92 (m, 1H), 6.89-6.83 (m, 1H) 6.01 (s, 1H); 5.39 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 463.0461 ($M+H$ $\text{C}_{21}\text{H}_{17}\text{BrF}_2\text{N}_2\text{O}_3$ requires 463.0463).

Example 156

2-([3-bromo-4-((2,4-difluorobenzyl)oxy)-6-methyl-2-oxopyridin-
 1(2H)-yl]methyl)benzamide



The title compound was prepared by a procedure essentially as described in Example 152 using the title compound of Example
 20 149 as starting material. ^1H NMR (400 MHz, CDCl_3) δ 7.68-7.66 (m, 2H), 7.57 (app q, $J = 8.4$ Hz, 1H); 7.42-7.34 (m, 2H); 6.98-6.92 (m, 1H), 6.89-6.83 (m, 1H) 6.01 (s, 1H); 5.39 (s, 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 463.0461 ($M+H$ $\text{C}_{21}\text{H}_{17}\text{BrF}_2\text{N}_2\text{O}_3$ requires 463.0463). ^1H NMR (400 MHz, CDCl_3) δ

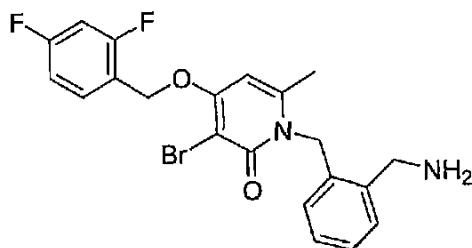
7.56-7.55 (m, 2H); 7.32-7.25 (m, 2H); 7.00-6.94 (m, 1H), 6.88-6.84 (m, 1H); 6.81-6.79 (m, 1H) 6.11 (s, 1H); 5.51 (s, 2H), 5.24 (s, 2H); 2.43 (s, 3H). ESHRMS m/z 463.0467 (M+H C₂₁H₁₇BrF₂N₂O₃ requires 463.0463).

5

Example 157

1-[2-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

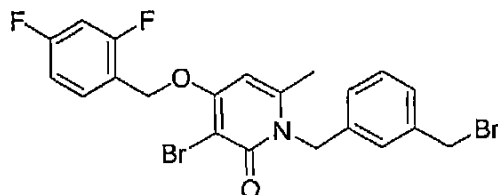
10



EXAMPLE 149 (50 mg, 0.11 mmol) was dissolved in tetrahydrofuran (2 mL) under N₂. Borane-methyl sulfide complex (0.11 mL, 0.22 mmol, 2M in tetrahydrofuran) was added. The reaction was then heated to 70°C and shaken overnight. After cooling to ambient temperature, all the solvent was distilled under vacuum. The resulting residue was partitioned between ethyl acetate and 0.2 N NaOH, and extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, washed with brine, and dried over Na₂SO₄, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid, to give product (19 mg, 39%). ¹H NMR (400 MHz, CDCl₃) δ 7.56-7.55 (m, 2H); 7.32-7.25 (m, 2H); 7.00-6.94 (m, 1H), 6.88-6.84 (m, 1H); 6.81-6.79 (m, 1H); 6.11 (s, 1H); 5.44 (s, 2H), 5.17 (s, 2H); 4.59 (s, 2H); 2.18 (s, 3H). ESHRMS m/z 449.0692 (M+H C₂₁H₁₉BrF₂N₂O₂ requires 449.0671).

Example 158

3-bromo-1-[3-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-
6-methylpyridin-2(1H)-one



5

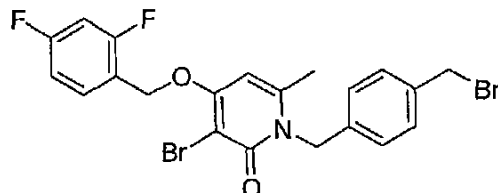
Preparation of 3-bromo-1-[3-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2 g, 6.06 mmol) was suspended in 1,4-dioxane (250 mL). α,α' -Dibromo-*m*-xylene (8 g, 30.3 mmol) was added followed by sodium hydride (0.3 g, 7.5 mmol, 60% in mineral oil). The reaction was heated to 60°C and stirred for 16 hours. The reaction was filtered through Celite® and the filtrate was concentrated to an oil that was partitioned between water and dichloromethane and extracted with dichloromethane (4 x 250 mL). The organic extracts were combined, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated to an oil, and purified by chromatography (silica gel, hexane/ethyl acetate) to yield a white solid (1.2g, 38%). ¹H NMR (400 MHz, CDCl₃) δ 7.57 (app q, *J* = 7.6 Hz, 1H); 7.28-7.25 (m, 2H); 7.17 (s, 1H); 7.08 (m, 1H); 6.94 (app dt, *J* = 1.2, 9.6 Hz, 1H), 6.87-6.82 (m, 1H); 5.99 (s, 1H), 5.34 (s, 2H), 5.20 (s, 2H); 4.43 (s, 2H); 2.29 (s, 3H). ES HRMS *m/z* 511.9672 (M+H C₂₁H₁₇Br₂F₂NO₂ requires 511.9667).

25

Example 159

3-bromo-1-[4-(bromomethyl)benzyl]-4-[(2,4-difluorobenzyl)oxy]-
6-methylpyridin-2(1H)-one



5

The title compound was prepared by a procedure essentially as described in Example 158. ¹H NMR (400 MHz, CDCl₃) δ 7.68-7.66 (m, 2H), 7.57 (app q, J = 8.4 Hz, 1H); 7.42-7.34 (m, 2H);

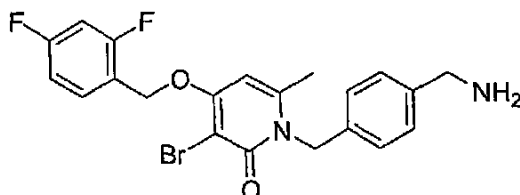
6.98-6.92 (m, 1H), 6.89-6.83 (m, 1H) 6.01 (s, 1H); 5.39 (s,

10 2H), 5.21 (s, 2H); 2.28 (s, 3H). ES HRMS m/z 463.0461 (M+H C₂₁H₁₇BrF₂N₂O₃ requires 463.0463). ¹H NMR (400 MHz, CDCl₃) δ 7.56 (app q, J = 7.6 Hz, 1H); 7.32 (d, J = 8.0 Hz, 2H); 7.14 (d, J = 8.0 Hz, 2H); 6.94 (app t, J = 8.4 Hz, 1H), 6.87-6.82 (m, 1H); 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 4.44 (s, 2H); 2.29 (s, 3H). ES HRMS m/z 511.9683 (M+H C₂₁H₁₇Br₂F₂NO₂ requires 511.9667).

15

Example 160

1-[4-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-
6-methylpyridin-2(1H)-one



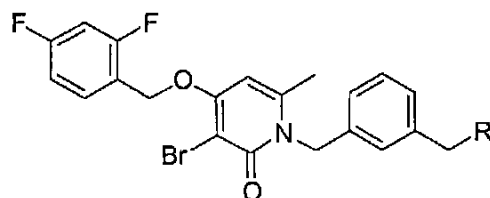
25

Example 159 (200 mg, 0.39 mmol) was suspended in methanol (3 mL) and cooled to -78 °C. Ammonia (g) was bubbled through the mixture for 30 minutes. The reaction vessel was sealed,

allowed to reach ambient temperature, and stirred for 4 hours. The solvent and ammonia were removed from the reaction in vacuo with stirring and the resulting oil was triturated with ether to yield a solid (174 mg, 99%). ^1H NMR (400 MHz, CD_3OD) δ 7.61 (q, $J = 7.6$ Hz, 1H); 7.40 (d, $J = 8.0$ Hz, 2H); 7.20 (d, $J = 8.0$ Hz, 2H); 7.03 (app t, $J = 8.8$ Hz, 2H), 6.51 (s, 1H), 5.43 (s, 2H), 5.29 (s, 2H); 4.07 (s, 2H); 2.36 (s, 3H). ES HRMS m/z 449.0673 ($\text{C}_{21}\text{H}_{19}\text{BrF}_2\text{N}_2\text{O}_2$ requires 449.0671).

10 Examples 161-168

The compounds of Examples 161-168 are prepared essentially according to the procedures set forth above for Examples 158-160 or by using the compound of Example 158:



15

Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 161	$-\text{NH}_2$	$\text{C}_{21}\text{H}_{19}\text{BrF}_2\text{N}_2\text{O}_2$	449.0671	449.0694
Ex. 162	morpholin-4-yl	$\text{C}_{25}\text{H}_{25}\text{BrF}_2\text{N}_2\text{O}_3$	519.1089	519.1132
Ex. 163	dimethylamino	$\text{C}_{23}\text{H}_{23}\text{BrF}_2\text{N}_2\text{O}_2$	477.0984	477.0991
Ex. 164	isopropylamino	$\text{C}_{24}\text{H}_{25}\text{BrF}_2\text{N}_2\text{O}_2$	491.1140	491.1121
Ex. 165	piperidin-1-yl	$\text{C}_{26}\text{H}_{27}\text{BrF}_2\text{N}_2\text{O}_2$	517.1297	517.1341
Ex. 166	(2-hydroxyethyl) amino	$\text{C}_{23}\text{H}_{23}\text{BrF}_2\text{N}_2\text{O}_3$	493.0933	493.0961
Ex. 167	bis(2-hydroxyethyl) amino	$\text{C}_{25}\text{H}_{27}\text{BrF}_2\text{N}_2\text{O}_4$	537.1195	537.1171
Ex. 168	piperazin-1-yl	$\text{C}_{25}\text{H}_{26}\text{BrF}_2\text{N}_3\text{O}_2$	518.1249	518.1280

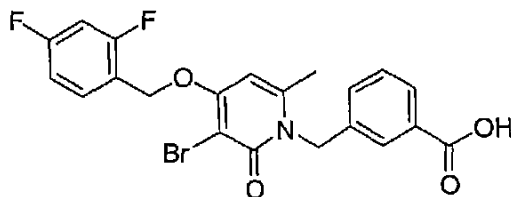
NMR characterization of compounds of Examples 161-168

Ex. No.	NMR Data
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Ex. 161	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 (q, J = 7.6 Hz, 1H); 7.42-7.35 (m, 2H), 7.24-7.20 (m, 2H), 7.03 (app t, J = 8.4 Hz, 2H), 6.51 (s, 1H), 5.43 (s, 2H), 5.29 (s, 2H); 4.07 (s, 2H); 2.04 (s, 3H)
Ex. 162	¹ H NMR (400 MHz, CD ₃ OD) δ 7.58 (app q, J = 7.6 Hz, 1H); 7.26-7.22 (m, 2H), 7.15 (s, 2H), 7.01 (app d, J = 6.4 Hz, 2H), 6.95 (app dt, J = 1.2, 8.0 Hz, 1H); 6.88-6.82 (m, 1H); 5.98 (s, 1H), 5.35 (s, 2H), 5.20 (s, 2H); 3.69 (t, J = 8.4 Hz, 4H); 3.46 (s, 2H); 2.41 (m, 4H); 2.29 (s, 3H)
Ex. 163	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 (app q, J = 7.6 Hz, 1H); 7.25-7.14 (m, 3H); 7.01-6.92 (m, 2H); 6.85 (m, 1H); 5.97 (s, 1H), 5.36 (s, 2H), 5.20 (s, 2H); 3.38 (s, 2H); 2.28 (s, 3H); 2.21 (s, 6H)
Ex. 164	¹ H NMR (400 MHz, CDCl ₃) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.25-7.22 (m, 2H); 7.14 (s, 1H), 6.99 (app d, 6.8 Hz, 1H), 6.94 (app dt, J = 2.0, 8.0 Hz, 1H), 6.88-6.80 (m, 1H); 5.97 (s, 1H), 5.34 (s, 2H), 5.19 (s, 2H); 3.73 (s, 2H); 2.28 (s, 3H); 2.82 (app heptet, J = 6.0 Hz, 1H), 1.07 (d, J = 6.0 Hz, 6H)
Ex. 165	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.27 (app t, J = 8.0 Hz, 1H); 7.20 (app d, J = 7.6 Hz, 1H); 7.08 (bs, 1H); 7.01 (app t, J = 8.0 Hz, 2H); 6.48 (s, 1H), 5.41 (s, 2H), 5.28 (s, 2H); 3.44 (s, 2H); 2.35 (s, 3H); 2.40-2.30 (m, 4H); 1.57-1.53 (m, 4H); 1.48-1.38 (m, 2H)
Ex. 166	¹ H NMR (400 MHz, CDCl ₃) δ 7.51 (app q, J = 8.0 Hz, 1H); 7.22-7.14 (m, 3H); 7.09 (bs, 1H); 6.98 (app d, J = 7.2 Hz, 1H); 6.89 (app dt, J = 1.6, 8.0 Hz, 1H); 6.81-6.76 (m, 1H); 5.92 (s, 1H), 5.28 (s, 2H), 5.14 (s, 2H); 3.73 (s, 2H); 3.59 (app t, J = 4.8 Hz, 2H); 2.73 (app t, J = 4.8 Hz, 2H); 2.24 (s, 3H)
Ex. 167	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.46 (app d, J = 8.8 Hz, 2H); 7.31 (bs, 1H); 7.27 (app t, J = 8.0 Hz, 1H); 7.03 (app t, J = 8.8 Hz, 2H); 6.54 (s, 1H), 5.44 (s, 2H), 5.30 (s, 2H); 4.47 (s, 2H); 3.90-3.84 (m, 4H); 3.40-3.25 (m, 4H); 2.40 (s, 3H)
Ex. 168	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 (app q, J = 8.0 Hz, 1H); 7.53-7.46 (m, 2H); 7.36 (bs, 1H); 7.30 (app d, J = 7.6 Hz, 1H); 7.05-7.01 (m, 2H); 6.55 (s, 1H), 5.44 (s, 2H), 5.30 (s, 2H); 4.47 (s, 2H); 3.58-3.53 (m, 8H); 2.42 (s, 3H)

Example 169

3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid

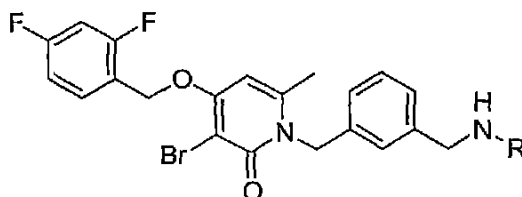


Preparation of 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid. EXAMPLE 154 (150 mg, 0.31 mmol) was dissolved in tetrahydrofuran (5 mL).

Potassium trimethylsilanolate (80 mg, 0.62 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated to an oil that was partitioned between water and ethyl acetate and extracted with ethyl acetate. The organic extracts were combined, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated to an oil and purified by reversed phase chromatography (C₁₈, 0.1% aqueous trifluoroacetic acid/acetonitrile) to yield the product (64 mg, 44%) ¹H NMR (400 MHz, CD₃OD) δ 7.92 (app d, J = 8.0 Hz, 1H); 7.78 (s, 1H); 7.62 (app q, J = 8.0 Hz, 1H); 7.44 (t, J = 7.6 Hz, 1H); 7.36 (app d, J = 8.0 Hz, 1H); 7.02 (app t, J = 7.6 Hz, 2H); 6.51 (s, 1H), 5.48 (s, 2H), 5.30 (s, 2H); 2.37 (s, 3H). ES HRMS m/z 464.0328 (C₂₁H₁₆BrF₂NO₄ requires 464.0304).

Examples 170-174

The compounds of Examples 170-174 are prepared using the compound of Example 159 or 161:



Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 170	-C(O)CH ₃	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₃	491.0776	491.0772
Ex. 171	-C(O)OCH ₃	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₄	507.0726	507.0731
Ex. 172	-SO ₂ CH ₃	C ₂₂ H ₂₁ BrF ₂ N ₂ O ₄ S	527.0446	527.0430
Ex. 173	-C(O)CH ₂ OH	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₄	507.0726	507.0712
Ex. 174	-C(O)NH ₂	C ₂₂ H ₂₀ BrF ₂ N ₃ O ₃	492.0729	492.0751

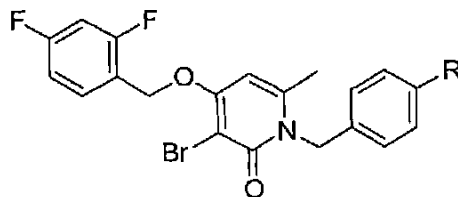
NMR characterization of compounds of Examples 170-174

Ex. No.	NMR Data
Ex. 170	¹ H NMR (400 MHz, CD ₃ OD) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.28 (app t, J = 8.0, 1H), 7.18 (app d, J = 8.0 Hz, 1H), 7.05-7.00 (m, 4H); 6.49 (s, 1H), 5.41 (s, 2H), 5.29 (s, 2H); 2.37 (s, 3H); 1.94 (s, 3H)
Ex. 171	¹ H NMR (400 MHz, CDCl ₃) δ 7.57 (app q, J = 7.6 Hz, 1H); 7.25 (app t, J = 8.0, 1H), 7.17 (app d, J = 8.0 Hz, 1H), 7.06-7.02 (m, 2H); 6.97-6.91 (m, 1H); 6.87-6.82 (m, 1H), 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 4.30 (d, J = 6.0 Hz, 2H); 3.67 (s, 3H); 2.28 (s, 3H)
Ex. 172	¹ H NMR (400 MHz, CD ₃ CN) δ 7.58 (app q, J = 7.6 Hz, 1H); 7.31 (app t, J = 8.0, 1H), 7.24 (app d, J = 8.0 Hz, 1H), 7.11 (s, 1H); 7.05-7.00 (m, 3H); 6.32 (s, 1H), 6.06 (bs, 1H), 5.31 (s, 2H), 5.23 (s, 2H); 4.17 (d, J = 6.4 Hz, 2H); 2.78 (s, 3H); 2.28 (s, 3H)
Ex. 173	¹ H NMR (400 MHz, CDCl ₃) δ 7.55 (app q, J = 8.0 Hz, 1H); 7.23 (app t, J = 7.6, 1H), 7.15 (app d, J = 7.2 Hz, 1H), 7.05-7.00 (m, 3H); 6.94 (app dt, J = 1.2, 8.8 Hz, 1H); 6.88-6.81 (m, 1H); 6.03 (s, 1H), 5.27 (s, 2H), 5.19 (s, 2H); 4.39 (d, J = 6.4 Hz, 2H); 4.05 (s, 2H), 2.31 (s, 3H)
Ex. 174	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 (app q, J = 8.0 Hz, 1H); 7.28 (app t, J = 8.0, 1H), 7.19 (app d, J = 8.0 Hz, 1H), 7.05-6.96 (m, 4H); 6.49 (s, 1H), 5.41 (s, 2H), 5.29 (s, 2H); 4.25 (s, 2H); 2.35 (s, 3H)

Examples 175-185

The compounds of Examples 175-175 are prepared using the

5 compounds of Examples 159 or 160:



Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 175	-CH ₂ NHCH(CH ₃) ₂	C ₂₄ H ₂₅ BrF ₂ N ₂ O ₂	491.1140	491.1143
Ex. 176	morpholin-4-ylmethyl	C ₂₅ H ₂₅ BrF ₂ N ₂ O ₃	519.1089	519.1062
Ex. 177	-CH ₂ N(CH ₃) ₂	C ₂₃ H ₂₃ BrF ₂ N ₂ O ₂	477.0984	477.0931
Ex. 178	piperidin-1-ylmethyl	C ₂₆ H ₂₇ BrF ₂ N ₂ O ₂	517.1297	517.1258

Ex. 179	[bis(2-hydroxyethyl)amino]methyl	$C_{25}H_{27}BrF_2N_2O_4$	537.1195	537.1181
Ex. 180	$-CH_2NHCH_2CH_2OH$	$C_{23}H_{23}BrF_2N_2O_3$	493.0933	493.0907
Ex. 181	piperazin-1-ylmethyl	$C_{25}H_{26}BrF_2N_3O_2$	518.1249	518.1213
Ex. 182	$-CH_2NHC(O)OCH_3$	$C_{23}H_{21}BrF_2N_2O_4$	507.0726	507.0752
Ex. 183	$-CH_2NHC(O)CH_3$	$C_{23}H_{21}BrF_2N_2O_3$	491.0776	491.0793
Ex. 184	$-CH_2NHSO_2CH_3$	$C_{22}H_{21}BrF_2N_2O_4S$	527.0446	527.0431
Ex. 185	$-CH_2NHC(O)NH_2$	$C_{22}H_{20}BrF_2N_3O_3$	492.0729	492.0720

NMR characterization of compounds of Examples 175-185

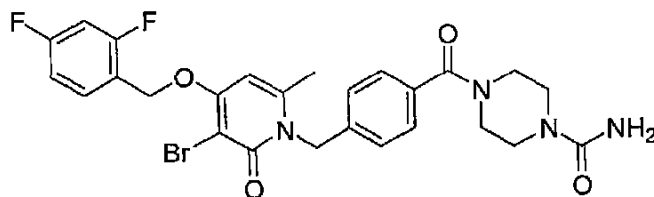
Ex. No.	NMR Data
Ex. 175	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, J = 8.0 Hz, 1H); 7.25 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.94 (app t, J = 8.0 Hz, 1H), 6.88-6.80 (m, 1H); 5.97 (s, 1H), 5.31 (s, 2H), 5.19 (s, 2H); 3.74 (s, 2H); 2.82 (app heptet, J = 6.0 Hz, 1H), 2.28 (s, 3H); 1.09 (d, J = 6.4 Hz, 6H)
Ex. 176	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, J = 8.0 Hz, 1H); 7.25 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.94 (app dt, J = 2.0, 8.0 Hz, 1H), 6.87-6.81 (m, 1H); 5.97 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 3.67 (app t, J = 4.8 Hz, 4H); 3.44 (s, 2H); 2.44-2.38 (m, 4H), 2.29 (s, 3H)
Ex. 177	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, J = 8.0 Hz, 1H); 7.23 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.93 (app dt, J = 2.0, 8.0 Hz, 1H), 6.86-6.81 (m, 1H); 5.96 (s, 1H), 5.33 (s, 2H), 5.18 (s, 2H); 3.38 (s, 2H); 2.29 (s, 3H); 2.20 (s, 6H)
Ex. 178	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (q, J = 8.0 Hz, 1H); 7.24-7.20 (m, 2H), 7.10-7.07 (m, 2H), 6.96-6.90 (m, 1H), 6.86-6.81 (m, 1H); 5.96 (s, 1H), 5.32 (s, 2H), 5.18 (s, 2H); 3.34 (s, 2H); 2.31 (s, 3H); 2.31-2.28 (m, 4H); 1.53-1.51 (m, 4H); 1.39 (m, 2H)
Ex. 179	1H NMR (400 MHz, $CDCl_3$) δ 7.57 (q, J = 8.0 Hz, 1H); 7.25 (d, J = 8.0 Hz, 2H); 7.12 (d, J = 8.0 Hz, 2H); 6.94 (dt, J = 8.8 Hz, 2H); 6.87-6.82 (m, 1H), 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 3.68 (s, 2H); 3.61 (t, J = 5.2 Hz, 4H); 2.70 (t, J = 5.2 Hz, 4H); 2.29 (s, 3H)
Ex. 180	1H NMR (400 MHz, $CDCl_3$) δ 7.57 (q, J = 8.0 Hz, 1H); 7.25 (d, J = 8.0 Hz, 2H); 7.12 (d, J = 8.0 Hz, 2H); 6.94 (app dt, J = 8.8 Hz, 2H); 6.87-6.82 (m, 1H), 5.98 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 3.68 (s, 2H); 3.61 (t, J = 5.2 Hz, 4H); 2.70 (t, J = 5.2 Hz, 4H); 2.29 (s, 3H)
Ex. 181	1H NMR (400 MHz, $CDCl_3$) δ 7.61 (q, J = 8.0 Hz, 1H); 7.52 (d, J = 8.0 Hz, 2H); 7.25 (d, J = 8.0 Hz, 2H); 7.03 (app t, J = 8.0 Hz, 2H); 6.53 (s, 1H), 5.44 (s, 2H), 5.30 (s, 2H); 4.32 (bs, 2H); 3.55-3.35 (m, 8H); 2.39 (s, 3H)

Ex. 182	¹ H NMR (400 MHz, CDCl ₃) δ 7.56 (app q, J = 8.0 Hz, 1H); 7.20 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.94 (app dt, J = 1.2, 8.0 Hz, 1H), 6.87-6.81 (m, 2H); 5.97 (s, 1H), 5.32 (s, 2H), 5.19 (s, 2H); 4.31 (d, J = 6.0 Hz, 2H); 3.68 (s, 3H); 2.28 (s, 3H)
Ex. 183	¹ H NMR (400 MHz, CDCl ₃) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.23 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 7.04-6.99 (m, 2H); 6.47 (s, 1H), 5.39 (s, 2H), 5.28 (s, 2H); 4.30 (s, 2H); 2.34 (s, 3H); 1.95 (s, 3H)
Ex. 184	¹ H NMR (400 MHz, CD ₃ OD) δ 7.62 (app q, J = 8.0 Hz, 1H); 7.34 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.02 (app t, J = 8.8 Hz, 2H), 6.48 (s, 1H), 5.42 (s, 2H), 5.28 (s, 2H); 4.21 (s, 2H); 2.82 (s, 3H); 2.35 (s, 3H)
Ex. 185	¹ H NMR (400 MHz, d ₇ DMF) δ 7.76 (app q, J = 8.0 Hz, 1H); 7.28 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.34-7.26 (m, 1H); 7.22-7.14 (m, 1H); 6.62 (s, 1H), 5.65 (s, 2H), 5.39 (s, 2H), 5.37 (s, 2H); 4.26 (d, J = 6.0 Hz, 2H); 2.40 (s, 3H)

Example 186

4-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-

5 oxopyridin-1(2H)-yl]methyl}benzoyl)piperazine-1-carboxamide

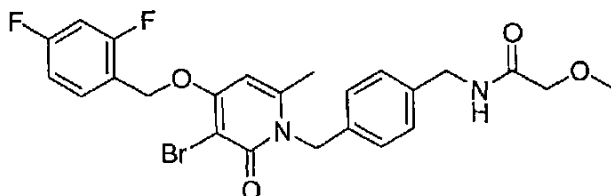


3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1H)-one (300 mg, 0.54 mmol) was dissolved in *N,N*-dimethylacetamide (5 mL). Trimethylsilyl isocyanate (0.15 mL, 1.08 mmol) was added followed by *N,N*-diisopropylethylamine (0.23 mL, 1.3 mmol) and the reaction was stirred for 1 hour at ambient temperature. The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1.3 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1.38 mmol/g) were added. The mixture was shaken for 6 hours, filtered, and the resulting filtrate was concentrated to a white solid (279 mg, 90%). ¹H NMR (400 MHz, CD₃OD) δ 7.61 (app q, J = 8.0 Hz, 1H); 7.41 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.03 (app t, J = 8.8 Hz, 2H); 6.51 (s, 1H), 5.46 (s, 2H), 5.30 (s, 2H), 3.75-3.35 (m, 8H);

2.37 (s, 3H). ES HRMS m/z 575.1104 ($C_{26}H_{25}BrF_2N_4O_4$ requires 575.1100).

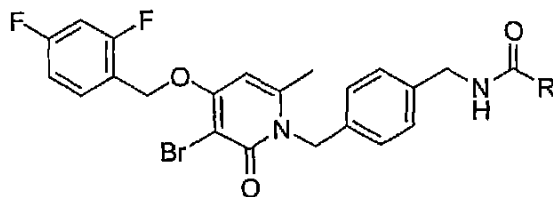
Example 187

5 N-(4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-methoxyacetamide



Polymer bound carbodiimide resin (2.3 g, 1.18 meq/g, 2.7 mmol) was suspended in *N,N*-dimethylformamide. Acetoxyacetic acid (120 mg, 1.33 mmol) was added, followed by 1-hydroxybenzotriazole (1M in *N,N*-dimethylformamide, 0.165 mL) and *N,N*-diisopropylethylamine (0.3 mL, 2.0 mmol). The reaction was shaken for 1 hour when EXAMPLE 159 (300 mg, 0.67 mmol) was added. The reaction was shaken for 16 hours and then diluted with tetrahydrofuran. Polyamine resin (1 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (2 g, 1.38 mmol/g) were added and the mixture was shaken for 72 hours, filtered and the resulting filtrate concentrated. Trituration with water followed by trituration with ether yielded a white solid (125 mg, 36%). 1H NMR (400 MHz, $CDCl_3$) δ 7.56 (app q, J = 8.0 Hz, 1H); 7.21 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.94 (app t, J = 8.8 Hz, 1H), 6.88-6.81 (m, 1H); 5.97 (s, 1H), 5.33 (s, 2H), 5.19 (s, 2H); 4.43 (d, J = 6.0 Hz, 2H); 3.92 (s, 2H); 3.39 (s, 3H); 2.29 (s, 3H). ES HRMS m/z 521.0882 ($C_{24}H_{22}BrF_2N_2O_4$ requires 521.0882).

Examples 188-193

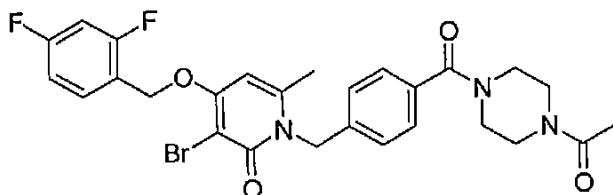


By following the general method for the preparation of Example 187 and substituting the appropriate carboxylic acid for
 5 acetoxymethoxyacetic acid, the compounds of Examples 188-193 are prepared. These compounds were triturated with water and again with ether and purified by chromatography (silica gel, hexane/ethyl acetate) as appropriate to yield off-white solids. Example 191 was prepared from its *N*-*t*-butoxycarbonyl
 10 protected intermediate. Deprotection was accomplished with 4N HCl in dioxane to afford the title compound as its hydrochloride salt (86 mg, 24%). Deprotection of the methyl ester from Ex. 188 was accomplished with K₂CO₃ in methanol/water to yield Ex. 192 as a white solid. The yields
 15 and analytical data are shown below.

Compound No.	R	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 188	CH ₂ OCOCH ₃	49	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₅	549.0831	549.0849
Ex. 189	C(CH ₃) ₂ OH	13	C ₂₅ H ₂₅ BrF ₂ N ₂ O ₄	535.1039	535.1035
Ex. 190	C(-CH ₂ CH ₂ -)) OH	33	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₄	535.0865	535.0876
Ex. 191	CH ₂ NH ₂	24	C ₂₃ H ₂₂ BrF ₂ N ₃ O ₃	533.0882	533.0899
Ex. 192	CH ₂ OH	25	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₄	507.0726	507.0730
Ex. 193	CH ₂ NHCOCH ₃	81	C ₂₅ H ₂₄ BrF ₂ N ₃ O ₃	548.0991	548.1000

Example 194

1-{4-[(4-acetylpiperazin-1-yl)carbonyl]benzyl}-3-bromo-4-
 [(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



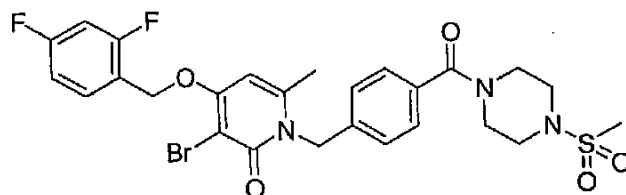
5

3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-
 1-ylcarbonyl)benzyl]pyridin-2(1H)-one (200 mg, 0.36 mmol) was
 dissolved in *N,N*-dimethylformamide (5 mL). *N,N*-
 Diisopropylethylamine (0.25 mL, 1.44 mmol) was added followed
 10 by acetic anhydride (0.10 mL, 1.06 mmol). The reaction was
 stirred for 2 hours at ambient temperature. and concentrated
 to an oil that was triturated in ether and again in water to
 yield an off-white solid (131 mg, 63%) ^1H NMR (400 MHz, CD_3OD)
 δ 7.62 (app q, $J = 8.0$ Hz, 1H); 7.42 (d, $J = 8.0$ Hz, 2H), 7.23
 15 (d, $J = 8.0$ Hz, 2H), 7.62-7.02 (m, 1H); 7.02 (app t, $J = 8.0$
 Hz, 1 H); 6.52 (s, 1H), 5.46 (s, 2H), 5.30 (s, 2H); 3.80-3.65
 (m, 8H); 2.37 (s, 3H); 2.11 (s, 3H). ES HRMS m/z 574.1150
 ($\text{C}_{27}\text{H}_{26}\text{BrF}_2\text{N}_3\text{O}_4$ requires 574.1148).

20 Example 195

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-{4-
 (methylsulfonyl)piperazin-1-yl]carbonyl}benzyl]pyridin-2(1H)-
 one

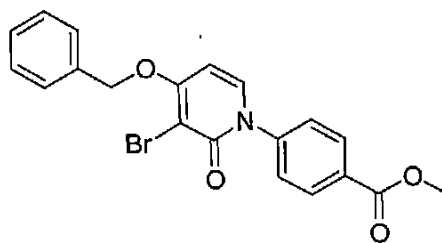
25



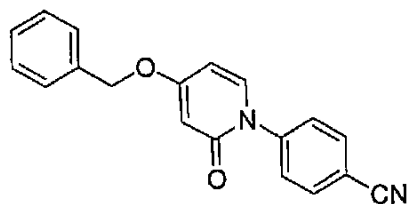
3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(piperazin-1-ylcarbonyl)benzyl]pyridin-2(1H)-one (300 mg, 0.54 mmol) was dissolved in *N,N*-dimethylformamide (5 mL). 4-Methylmorpholine (0.23 mL, 2.2 mmol) was added followed by methanesulfonyl chloride (0.10 mL, 1.33 mmol) and the reaction was stirred for 2 h. The reaction was then diluted with tetrahydrofuran (40 mL) and polyamine resin (1.3 g, 2.81 mmol/g) and methylisocyanate functionalized polystyrene (1 g, 1.38 mmol/g) were added. The mixture was shaken for 16 hours, filtered, and the resulting filtrate concentrated to an oil that was triturated with water. The resulting white solid was collected, washed with ether and dried (172 mg, 52%). ¹H NMR (400 MHz, CDCl₃) δ 7.57 (app q, *J* = 8.2 Hz, 1H); 7.34 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.02 (app dt, *J* = 1.2, 8.8 Hz, 1H), 6.88-6.82 (m, 1H); 6.02 (s, 1H), 5.37 (s, 2H), 5.21 (s, 2H); 3.80-3.20 (m, 8H); 2.79 (s, 3H); 2.30 (s, 3H). ES HRMS *m/z* 610.0851 (C₂₆H₂₆BrF₂N₃O₅S requires 610.0817).

Example 196

Methyl-4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoate.

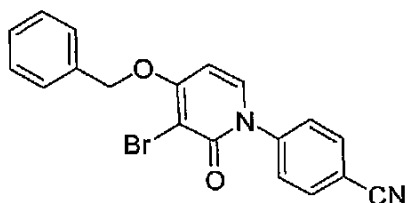


Step 1. Preparation of 4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile.



4-benzyloxy-2(1H)-pyridone (12.00 g, 59.63 mmol) was dissolved in dimethyl sulfoxide (100 mL). Potassium carbonate (10.99 g, 79.50 mmol) was added, followed by 4-fluorobenzonitrile (4.81 g, 39.75 mmol). The reaction was stirred at 100 °C for 18 hours. After cooling to room temperature the reaction was diluted with H₂O (150 mL) and the solids were collected by filtration washing with diethyl ether. Chromatography (silica gel, hexanes/ethyl acetate) provided an off-white solid (7.78 g, 65%). ¹H NMR (300 MHz, CDCl₃) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.44-7.41 (m, 5H), 7.22 (d, *J* = 13.3, 1H), 6.13 (dd, *J* = 2.6, 7.7 Hz, 1H), 6.06 (d, *J* = 2.6 Hz, 1H), 5.07 (s, 2H).

Step 2. Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile .



4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile (Step 1) (2.76 g, 9.13 mmol) was suspended in acetonitrile (50 mL) and cooled in an ice-bath. *N*-bromosuccinimide (1.71 g, 9.54 mmol) was added. Once the addition was complete the cooling bath was removed. After stirring for 45 minutes the reaction was diluted with acetonitrile and solids were collected by

filtration to give a white solid (3.13 g, 90%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.00 (d, $J = 8.5$ Hz, 2H), 7.84 (d, $J = 7.9$ Hz, 1H), 7.66 (d, $J = 8.5$, 2H), 7.50-7.37 (m, 5H), 6.63 (d, $J = 7.9$ Hz, 1H), 5.41 (s, 2H).

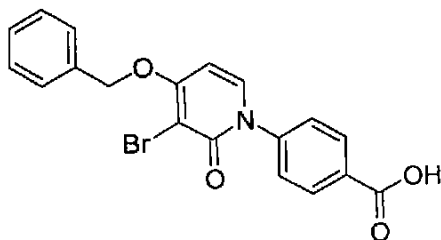
5

Step 3. Preparation of methyl-4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoate. 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzonitrile (Step 2) (1.50 g, 3.93 mmol) suspended in methanol (50 mL) was cooled in an ice-bath. HCl (g) was then bubbled through the mixture for 5 minutes. The reaction was then stirred at room temperature overnight, at which time the reaction mixture was concentrated. The residue was suspended in 6N HCl (60 mL) and heated at reflux for 1.5 hours. After cooling to room temperature the solids were collected by filtration. Chromatography (silica gel, hexanes/ethyl acetate) provided an off-white shiny solid (0.540 g, 61%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.04 (d, $J = 8.5$ Hz, 2H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 8.6$ Hz, 2H), 7.47-7.39 (m, 5H), 6.57 (d, $J = 7.9$ Hz, 1H), 5.38 (s, 2H), 3.86 (s, 3H). ES-HRMS m/z 416.0355 ($M+H$ calcd for $\text{C}_{20}\text{H}_{16}\text{BrNO}_4$ requires 414.0341).

20

Example 197

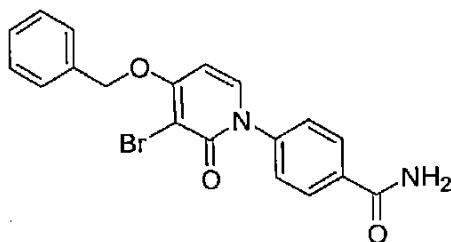
25 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoic acid.



Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzoic acid. EXAMPLE 196 (0.460 g, 1.11 mmol) was dissolved in tetrahydrofuran (5.0 mL). Potassium trimethylsilanolate (0.285 g, 2.22 mmol) was added. The reaction was stirred at room temperature for 3 hours at which time H₂O (10 mL) was added. The aqueous reaction mixture was acidified (pH-3) with 1N HCl. The tetrahydrofuran was evaporated, additional H₂O (50 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated to provide a rust colored solid (0.444 g, 100%). ¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.50-7.34 (m, 5H), 6.57 (d, J = 7.9 Hz, 1H), 5.38 (s, 2H). ES-HRMS m/z 400.0191 (M+H calcd for C₁₉H₁₄BrNO₄ requires 400.0184).

Example 198

4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzamide.

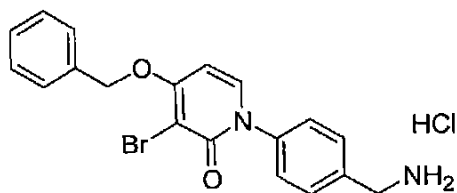


Preparation of 4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzamide. STEP 2, EXAMPLE 196 (0.238 g, 0.624 mmol) was suspended in tert-butyl alcohol (3.0 mL). KF on 40 wt % Al₂O₃ (0.453 g, 3.12 mmol) was added. The reaction mixture was heated at reflux for 5 days. Additional KF on 40 wt % Al₂O₃ (0.453 g, 3.12 mmol) was added and heating was continued at reflux overnight. After cooling to room temperature

chloroform and methanol were added and the solids were collected by filtration. Chromatography (reverse-phase, acetonitrile/H₂O) provided a tan solid (0.073 g, 30%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.47-7.34 (m, 7H), 6.56 (d, *J* = 7.9 Hz, 1H), 5.38 (s, 2H). ES-HRMS *m/z* 399.0372 (*M*+*H* calcd for C₁₉H₁₅BrN₂O₃ requires 399.0344).

Example 199

1- [4- (aminomethyl)phenyl] -4- (benzyloxy) -3-bromopyridin-2 (1H) - one.



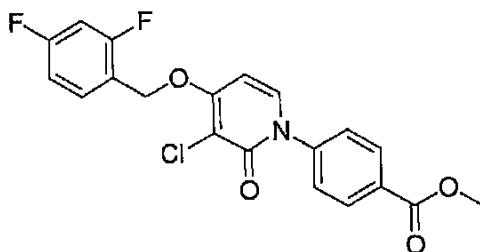
Preparation of 1- [4- (aminomethyl)phenyl] -4- (benzyloxy) -3-bromopyridin-2 (1H) -one. STEP 2, EXAMPLE 196 (1.25 g, 3.28 mmol) was dissolved in tetrahydrofuran (15 mL). Borane-dimethylsulfide (3.44 mL, 6.89 mmol, 2.0 M in tetrahydrofuran) was added and the mixture heated at reflux. After 14.5 hours the solvent was evaporated. 0.5M NaOH (50 mL) was added followed by ethyl acetate. The aqueous layer was neutralized with 1N HCl. Methanol saturated with HCl was added and the mixture was heated at reflux for 5 hours. After cooling to room temperature, diethyl ether was added and the solids were collected by filtration. The solids were treated with 4N HCl in dioxane (5 mL) and methanol (1 mL) at room temperature for 1 hour, at which time diethyl ether was added and the solids were collected by filtration to give a tan solid (0.920 g,

67%). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.67 (br s, 2H), 7.76 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.3 Hz, 2H), 7.50-7.37 (m, 7H), 6.56 (d, J = 7.6 Hz, 1H), 5.41 (s, 2H), 4.09 (br s, 2H). ES-
HRMS m/z 385.0555 ($M+H$ calcd for $\text{C}_{19}\text{H}_{17}\text{BrN}_2\text{O}_2$ requires

5 385.0552).

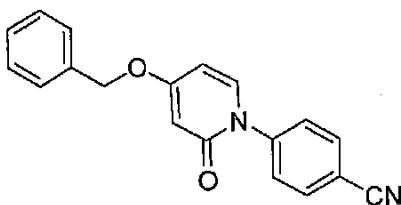
Example 200

Methyl-4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxypyridin-
10 1(2H)-yl]benzoate.



Step 1. Preparation of 4-[4-(benzyloxy)-2-oxypyridin-1(2H)-
yl]benzonitrile.

15

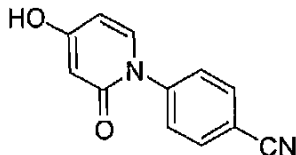


4-benzyloxy-2(1H)-pyridone (50.0 g, 248.47 mmol) was dissolved
in dimethyl sulfoxide (300 mL). Potassium carbonate (68.68 g,
496.94 mmol) was added, followed by 4-fluorobenzonitrile
20 (31.60 g, 260.89 mmol). The reaction was stirred at 100 °C for
20 hours. After cooling to room temperature the reaction was
diluted with H_2O (600 mL) and the solids were collected by
filtration washing with diethyl ether. The solids were then
washed with hot methanol to provide a tan solid (55.6 g, 74%).

25 ^1H NMR (300 MHz, CDCl_3) δ 7.79 (d, J = 8.3 Hz, 2H), 7.54 (d, J

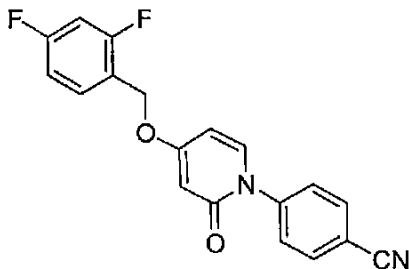
= 8.5 Hz, 2H), 7.44-7.41 (m, 5H), 7.22 (d, J = 13.3, 1H), 6.13 (dd, J = 2.6, 7.7 Hz, 1H), 6.06 (d, J = 2.6 Hz, 1H), 5.07 (s, 2H).

- 5 Step 2. Preparation of 1-[4-nitrilephenyl]-4-hydroxy-2(1H)-pyridinone.



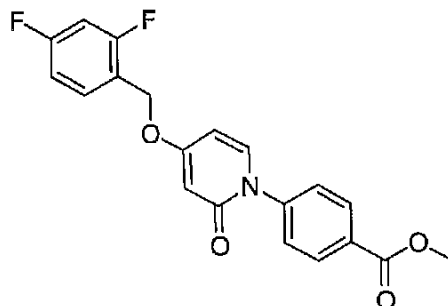
- 4-[4-(benzyloxy)-2-oxopyridin-1(2H)-yl]benzonitrile (Step 1)
10 (20.0 g, 66.15 mmol) was dissolved in methanol (300 mL). Ammonium formate (8.34 g, 132.3 mmol) was added followed by 5% Pd/C (6.62 g). The resulting mixture was heated at reflux for 20 minutes at which time the reaction began to exotherm. The reaction was allowed to cool to room temperature at which time
15 it was filtered through a pad of Celite® washing with methanol. The filtrate was evaporated to provide a pale yellow solid (16.2 g, >100%). ^1H NMR (300 MHz, CDCl_3) δ 8.46 (s, 1H), 7.95 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 7.7 Hz, 1H), 5.98 (dd, J = 2.6, 7.7 Hz, 1H), 5.54
20 (d, J = 2.4 Hz, 1H).

Step 3. Preparation of 4-[4-[(2,4-difluorobenzyloxy)]-2-oxopyridin-1(2H)-yl]benzonitrile.



1-[4-Nitrilephenyl]-4-hydroxy-2(1H)-pyridinone (Step 2) (16.2 g) was dissolved in *N,N*-dimethylformamide (100 mL). Potassium carbonate (10.06 g, 72.77 mmol) was added followed by α -bromo-2,4-difluorotoluene (8.91 mL, 69.46 mmol). The resulting
5 mixture was heated to 65°C for 1 hour. Additional α -bromo-2,4-difluorotoluene (4.25 mL, 33.08 mmol) was added. The resulting mixture was heated to 65°C for 5 hours. Additional α -bromo-2,4-difluorotoluene (2.12 mL, 16.54 mmol) was added. After stirring at 65°C overnight the reaction was allowed to
10 cool to room temperature. H₂O (300 mL) was added and the solid was collected by filtration. A portion (8.0 g) of the solids were washed with hot methanol to give a pale yellow solid (6.22 g, 78%). ¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.72-7.64 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.40-7.32
15 (m, 1H), 7.22-7.16 (m, 1H), 6.17-6.11 (m, 2H), 5.17 (s, 2H).

Step 4. Preparation of methyl-4-[4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]benzoate.



20

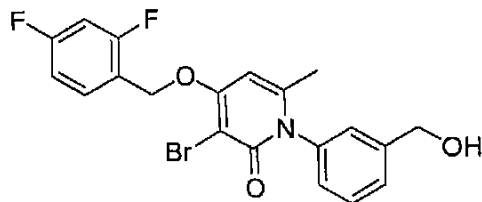
4-[4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]benzonitrile (Step 3) (2.00 g, 5.91 mmol) suspended in methanol (20 mL) and H₂O (5 mL) was cooled in an ice-bath. HCl
25 (g) was bubbled through the mixture until most of the solids dissolved. The resulting mixture was then heated at reflux for 3 hours. The reaction was then recooled in an ice-bath

and HCl was bubbled through the mixture for 5 minutes. The mixture was heated at reflux for 2 hours and then the methanol was evaporated. Additional H₂O (50 mL) was added and the aqueous reaction mixture was extracted with ethyl acetate (50 mL) and tetrahydrofuran (50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated. Chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) gave an off-white solid (0.630 g, 29%). ¹H NMR (300 MHz, DMF-d₆) δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.80 (app q, *J* = 7.9 Hz, 1H), 7.74-7.67 (m, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.42-7.34 (app dt, *J* = 2.4, 9.0 Hz, 1H), 7.28-7.22 (m, 1H), 6.20 (dd, *J* = 2.6, 7.6 Hz, 1H), 6.15 (d, *J* = 2.4 Hz, 1H), 5.28 (s, 2H), 3.98 (s, 3H).

Step 5. Preparation of methyl-4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxypyridin-1(2H)-yl]benzoate. Methyl-4-[4-[(2,4-difluorobenzyl)oxy]-2-oxypyridin-1(2H)-yl]benzoate (Step 4) (0.520 g, 1.40 mmol) was suspended in acetonitrile (10.0 mL). *N*-chlorosuccinimide (0.196 g, 1.47 mmol) was added followed by several drops of dichloroacetic acid. The resulting mixture was heated at reflux overnight. After cooling to room temperature additional acetonitrile was added and the precipitate was collected by filtration to give an off-white solid (0.331 g, 58%). ¹H NMR (300 MHz, DMF-d₆) δ 8.34 (d, *J* = 8.5 Hz, 2H), 8.12 (d, *J* = 7.9 Hz, 1H), 8.04-7.96 (m, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.59-7.53 (m, 1H), 7.52-7.41 (m, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 5.70 (s, 2H), 4.15 (s, 3H). ES-HRMS *m/z* 406.0644 (*M*+H calcd for C₂₀H₁₄ClF₂NO₄ requires 406.0652).

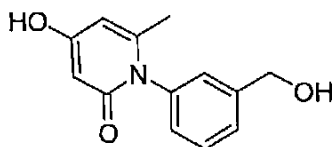
Example 201

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one.



5

Step 1. Preparation of 4-Hydroxy-1-[3-(hydroxymethyl)phenyl]6-methylpyridin-2(1H)-one.

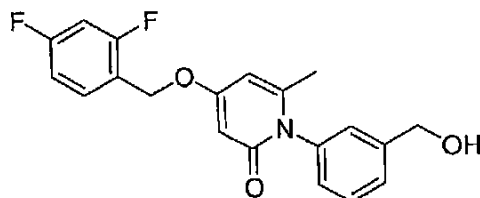


10

4-hydroxy-6-methyl-2-pyrone (10.0 g, 79.3 mmol) and 3-aminobenzyl alcohol (9.77g, 79.3 mmol) were combined in H₂O (100 mL) and heat at reflux. After 48 hours at reflux the reaction mixture was concentrated. The residue was treated with methanol and the precipitate was collected by filtration to give a pale yellow solid (3.04 g, 17%). ¹H NMR (300 MHz, DMSO-d₆) δ 10.6 (br s, 1H), 7.46-7.35 (m, 2H), 7.09-7.03 (m, 2H), 5.88 (d, J = 1.6 Hz, 1H), 5.55 (d, J = 2.6 Hz, 1H), 4.54 (d, J = 4.2 Hz, 2H), 1.83 (s, 3H).

20

Step 2. Preparation of 1-[3-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.



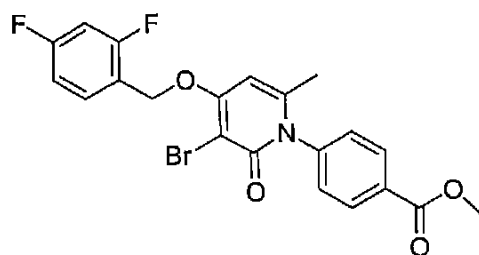
4-Hydroxy-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one (Step 1) (0.674 g, 2.91 mmol) was suspended in acetone (10 mL). Cesium carbonate (1.04 g, 3.21 mmol) was added followed by α -bromo-2,4-difluorotoluene (0.392 mL, 3.06 mmol). After stirring at room temperature for 2 days the reaction was concentrated. The residue was portioned between H₂O (30 mL) and ethyl acetate (30 mL). The aqueous layer was further extracted with ethyl acetate (30 mL). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated. Chromatography (on silica, hexanes/ethyl acetate with 10% methanol) provided a white solid (0.531 g, 51%). ¹H NMR (300 MHz, CDCl₃) δ 7.51-7.39 (m, 3H), 7.82 (s, 1H), 7.16 (d, *J* = 26.8 Hz, 1H), 7.08-6.86 (m, 2H), 6.00 (d, *J* = 2.6 Hz, 1H), 5.92 (d, *J* = 2.6 Hz, 1H), 5.05 (s, 2H), 4.68 (s, 2H), 1.93 (s, 3H). ES-HRMS *m/z* 358.1256 (*M*+*H* calcd for C₂₀H₁₇F₂NO₃ requires 358.1249).

Step 3. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one. 1-[3-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Step 2) (0.460 g, 1.29 mmol) was suspended in acetonitrile (5.0 mL) and cooled in an ice-bath. *N*-bromosuccinimide (0.241 g, 1.35 mmol) was added. Once the addition was complete the cooling bath was removed. After stirring for 1.5 hours the reaction was diluted with acetonitrile and solids were collected by filtration to give a white solid (0.385 g, 68%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.70 (app q, *J* = 7.9 Hz, 1H), 7.49-7.32 (m, 3H), 7.24-7.10 (m, 3H), 6.66 (s, 1H), 5.35 (s, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 1.95 (s, 3H). ES-HRMS *m/z* 436.0384 (*M*+*H* calcd for C₂₀H₁₆BrF₂NO₃ requires 436.0354).

Example 202

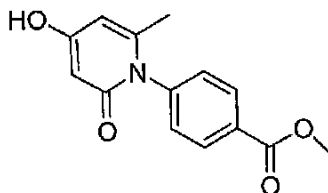
Methyl-4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-

5 oxopyridin-1(2H)-yl]benzoate.



Step 1. Preparation of Methyl 4-(4-hydroxy-6-methyl-2-

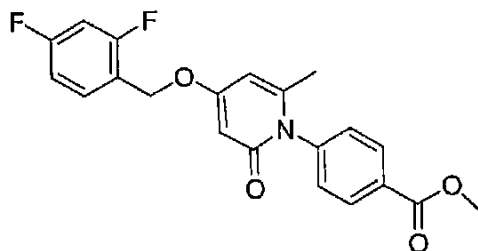
10 oxopyridin-1(2H)-yl]benzoate.



4-hydroxy-6-methyl-2-pyrone (21.00 g, 166.70 mmol) and 4-
15 methylaminobenzoate (25.20 g, 166.70 mmol) were combined in
1,2-dichlorobenzene (50 mL) and rapidly heated to 160 °C.
After 15 minutes at 160 °C the reaction was allowed to cool to
room temperature. The reaction was diluted with
dichloromethane (50 mL) and extracted with saturated Na₂CO₃ (2
20 x 100 mL). The combined aqueous layers were acidified (pH-2)
with concentrated HCl. The precipitate was collected by
filtration and washed with diethyl ether to give a
yellow/orange solid (10.9 g, 25%). ¹H NMR (300 MHz, DMSO-*d*₆) δ
10.8 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz,

2H), 5.95 (d, $J = 2.4$ Hz, 1H), 5.61 (d, $J = 2.4$, 1H), 3.91 (s, 3H), 1.85 (s, 3H).

Step 2. Preparation of Methyl-4-[4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate.



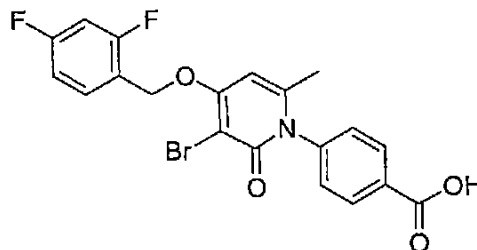
Methyl 4-(4-hydroxy-6-methyl-2-oxypyridin-1(2H)-yl)benzoate
(Step 1) (10.90 g, 42.04 mmol) was dissolved in *N,N*-
dimethylformamide (100 mL). Potassium carbonate (6.97 g,
50.45 mmol) was added, followed by 2,4-difluorobenzyl bromide
(5.66 mL, 44.14 mmol). The reaction was stirred at room
temperature for 3 days then diluted with H₂O (100 mL). The
reaction mixture was extracted into ethyl acetate and
tetrahydrofuran (2 x 100 mL). The precipitate was collected
by filtration and the organic filtrate was washed with brine
(50 mL), dried over Na₂SO₄, filtered and evaporated. The
resulting solid was combined with the precipitate to provide a
pale pink solid (6.77 g, 42%). ¹H NMR (300 MHz, DMSO-*d*₆)
δ 8.01 (d, $J = 8.3$ Hz, 2H), 7.67 (q, $J = 7.9$ Hz, 1H), 7.43 (d,
 $J = 8.3$ Hz, 2H), 7.35 (m, 1H), 7.18 (*app* dt, $J = 1.6, 8.5$ Hz,
1H), 6.08 (d, $J = 1.8$ Hz, 1H), 5.98 (d, $J = 2.4$ Hz, 1H), 5.14
(s, 2H), 3.91 (s, 3H), 1.87 (s, 3H).

Step 3. Preparation of methyl-4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate.
Methyl-4-[4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-

yl]benzoate (Step 2) (6.74 g, 17.49 mmol) suspended in acetonitrile (100 mL) was cooled in an ice-bath. N-bromosuccinimide (3.27 g, 18.36 mmol) was added. After 1 hour the ice-bath was removed and after an additional 30 minutes the reaction was diluted with acetonitrile (20 mL). The precipitate was collected by filtration to provide the title compound as an off-white solid (6.94 g, 85%). ¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 8.7 Hz, 2H), 7.61 (q, J = 7.9 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.02-6.96 (m, 1H), 6.90 (app dt, J = 2.4, 9.5 Hz, 1H), 6.14 (s, 1H), 5.28 (s, 2H), 3.98 (s, 3H), 2.00 (s, 3H). ES-HRMS m/z 464.0304 (M+H calcd for C₂₁H₁₆BrF₂NO₄ requires 464.0301).

Example 203

4-[3-bromo-4-[(difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid.



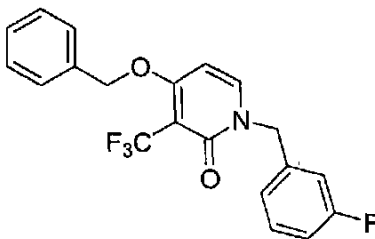
EXAMPLE 202 (7.43 g, 16.00 mmol) was dissolved in tetrahydrofuran (40 mL). Potassium trimethylsilanolate (4.10 g, 32.00 mmol) was added and the reaction mixture was stirred at room temperature for 22 hours. The tetrahydrofuran was evaporated and H₂O (50 mL) was added. The aqueous reaction mixture was acidified with 1N HCl and the precipitate was collected by filtration. The solids were washed with boiling methanol to give an off-white solid (5.05 g, 70%). ¹H NMR

(300 MHz, DMSO- d_6) δ 13.2 (br s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.72 (q, J = 7.9 Hz, 1H), 7.45 (d, J = 8.3 Hz, 2H), 7.38 (app dt, J = 2.4, 9.9 Hz, 1H), 7.23 (app dt, J = 1.8, 8.5 Hz, 1H), 6.72 (s, 1H), 5.37 (s, 2H), 1.97 (s, 3H). ES-HRMS m/z

5 450.0154 (M+H calcd for $C_{20}H_{14}BrF_2NO_4$ requires 450.0147).

Example 204

4-(Benzyloxy)-1-(3-fluorobenzyl)-3-(trifluoromethyl)pyridin-
10 2(1H)-one.

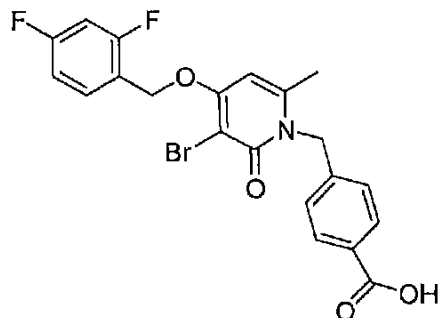


The starting material (0.250 g, 0.591 mmol) was dissolved in 1-methyl-2-pyrrolidinone (5.0 mL). Trifluoroacetic acid, sodium salt (0.322 g, 2.36 mmol) was added, followed by
15 copper(I)iodide (0.225 g, 1.18 mmol). The resulting mixture was heated to 180°C for 5 hours and then allowed to cool to room temperature. The reaction was diluted with H_2O (50 mL) and brine (50 mL), then extracted into ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (50
20 mL), dried over Na_2SO_4 , filtered and evaporated.

Chromatography (reverse-phase, acetonitrile/ H_2O) provided an off-white solid (0.050 g, 22%). 1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.27 (m, 8H), 7.06 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 6.07 (d, J = 7.7 Hz, 1H), 5.20 (s, 2H), 5.06 (s, 2H).
25 ES-HRMS m/z 378.1097 (M+H calcd for $C_{20}H_{15}F_4NO_2$ requires 378.1112).

Example 205

4-{ [3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoic acid

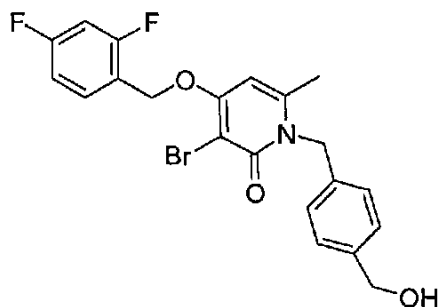


5

EXAMPLE 153 (50.0 g, 104.54 mmol) was dissolved in methanol (500 mL) and dioxane (100 mL). 1N NaOH (130 mL, 130 mmol) was added. The resulting mixture was heated to 50 °C for 5.5
 10 hours. The reaction was partially concentrated and the heterogenous mixture was acidified (pH 2) with 1N HCl. The precipitate was collected by filtration to afford a white solid (49.2 g, >100 %). ¹H NMR (300 MHz, DMSO-d₆) δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.70 (app q, *J* = 7.9 Hz, 1H), 7.35 (dt, *J* = 2.2, 9.9 Hz, 1H), 7.18 (app d, *J* = 8.3 Hz, 2H), 7.17-7.12 (m, 1H), 6.64 (s, 1H), 5.41 (s, 2H), 5.33 (s, 2H), 2.32 (s, 3H).
 15 ES-HRMS *m/z* 464.0327 (M+H calcd for C₂₁H₁₆BrF₂NO₄ requires 464.0304).

20 Example 206

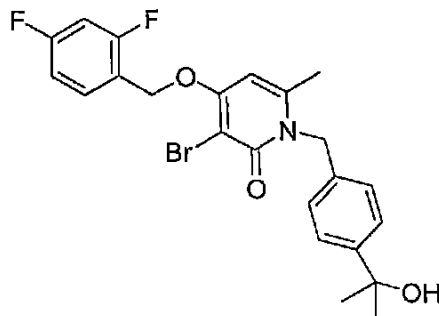
3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(hydroxymethyl)benzyl]-6-methylpyridin-2(1H)-one.



Example 205 (40.0 g, 86.16 mmol) suspended in tetrahydrofuran (300 mL) was cooled in an ice-bath. Borane dimethylsulfide (129.2 mL, 258.48 mmol, 2.0 M in tetrahydrofuran) was slowly added. The resulting mixture was slowly allowed to warm to room temperature overnight. The mixture was recooled in an ice-bath and quenched by the addition of small pieces of ice. After the evolution of gas ceased additional ice-water was added. The flask was fitted with a distillation apparatus and the dimethylsulfide was removed. After the reaction was cooled to room temperature, H₂O (300 mL), ethyl acetate (200 mL) and tetrahydrofuran (300 mL) were added. The precipitate that formed was collected by filtration and the filtrate was placed in a separatory funnel. The aqueous layer was further extracted with ethyl acetate (300 mL). The combined organic layers were washed with brine (300 mL). The organic phase was dried over Na₂SO₄ and evaporated which was combined with the precipitate to yield an off-white solid (37.8 g, 97%). ¹H NMR (400 MHz, CDCl₃) δ 7.47 (app q, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.86 (app dt, *J* = 2.3, 8.6 Hz, 1H), 6.79 (app dt, *J* = 2.4, 8.4 Hz, 1H), 6.00 (s, 1H), 5.28 (s, 2H), 5.16 (s, 2H), 4.57 (s, 2H), 2.25 (s, 3H). ES-
HRMS *m/z* 450.0512 (M+H calcd for C₂₁H₁₈BrF₂NO₃ requires 450.0511).

Example 207

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)benzyl]-6-methylpyridin-2(1H)-one.



5 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1-hydroxy-1-methylethyl)benzyl]-6-methylpyridin-2(1H)-one.

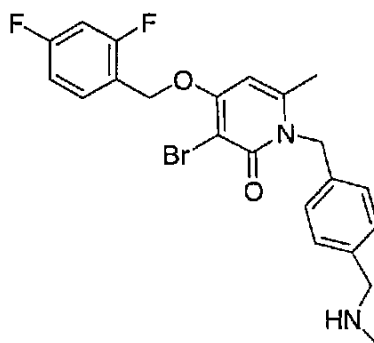
EXAMPLE 153 (2.00 g, 4.18 mmol) suspended in tetrahydrofuran (20 mL) was cooled in the dry ice/acetone bath. Methyl magnesium bromide (4.32 mL, 12.96 mmol, 3.0 M in diethyl ether) was slowly added. The reaction was slowly allowed to
 10 warm to room temperature overnight. The reaction was then cooled in an ice bath and quenched by the addition of saturated NH_4Cl (50 mL). H_2O was added and the reaction was extracted with ethyl acetate. The combined organic layers
 15 were washed with brine, dried over Na_2SO_4 , filtered and evaporated. The residue was subjected to chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) to provide an off-white foam. The foam was dissolved in acetonitrile and cooled in an ice bath. *N*-bromosuccinimide
 20 (0.057 g, 0.320 mmol) was added. Once the addition was complete the cooling bath was removed. After 2.5 hours at room temperature the reaction was concentrated. Purification by chromatography (silica gel, hexanes/ethyl acetate with 10% methanol) provided a white foam. ^1H NMR (400 MHz, CDCl_3) δ
 25 7.56 (app q, $J = 7.7$ Hz, 1H), 7.39 (d, $J = 78.3$ Hz, 2H), 7.11 (d, $J = 8.2$ Hz, 2H), 6.92 (app dt, $J = 1.7, 8.4$ Hz, 1H), 6.86-6.81 (m, 1H), 5.97 (s, 1H), 5.31 (s, 2H), 5.18 (s, 2H), 2.29

(s, 3H), 1.52 (s, 6H). ES-HRMS m/z 478.0811 (M+H C₂₃H₂₂BrF₂NO₃ requires 478.0824).

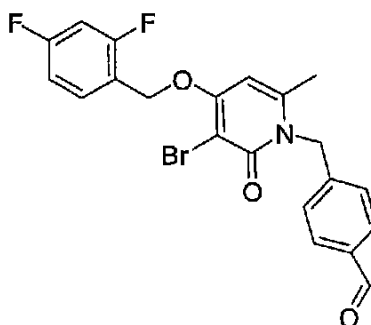
Example 208

5

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-[(methylamino)methyl]benzyl]pyridin-2(1H)-one.



10 Step 1. Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzaldehyde.



15

EXAMPLE 206 (1.30 g, 2.89 mmol) was suspended in acetonitrile (10 mL) and cooled in an ice-bath. 1-hydroxy-1,3-dihydro-3,3-bis(trifluoromethyl)-1,2-benziodoxole 1-oxide (0.580 g, 1.44 mmol) was added and the reaction mixture was stirred at room temperature overnight. Diethyl ether was added and the solid was collected by filtration to give a white solid (1.14 g,

20

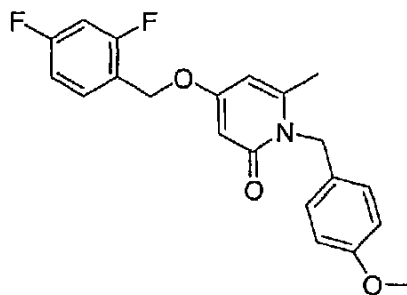
88%). ¹H NMR (400 MHz, CDCl₃) δ 9.96 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.56 (app q, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 6.93 (app dt, *J* = 1.6, 8.3 Hz, 1H), 6.87-6.82 (m, 1H), 6.02 (s, 1H), 5.41 (s, 2H), 5.20 (s, 2H), 2.27 (s, 3H).

5

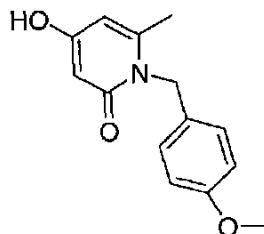
Step 2. 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[4-[(methylamino)methyl]benzyl]pyridin-2(1H)-one. 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzaldehyde (Step 1) (1.53 g, 3.41 mmol) of step 1
10 was dissolved in *N,N*-dimethylformamide (5.0 mL). Methylamine (3.41 mL, 6.83 mmol, 2.0 M in tetrahydrofuran) was added followed by NaHB(OAc)₃ (2.17 g, 10.23 mmol) in *N,N*-dimethylformamide (8.0 mL) and acetic acid (2.0 mL). The reaction was stirred at room temperature overnight at which
15 time 1N NaOH (50 mL) was added and then extracted with ethyl acetate (2 x 50 mL). The organic layers were washed with brine (25 mL), dried over Na₂SO₄ and evaporated. Chromatography (on silica, ethyl acetate with 5% methanolic ammonia/hexanes) afforded a tan solid (0.810 g, 53%). ¹H NMR
20 (400 MHz, CDCl₃) δ 7.55 (app q, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.92 (app dt, *J* = 2.4, 8.3 Hz, 1H), 6.90-6.80 (m, 1H), 5.95 (s, 1H), 5.32 (s, 2H), 5.17 (s, 2H), 3.68 (s, 2H), 2.40 (s, 3H), 2.27 (s, 3H). ES-
25 HRMS *m/z* 463.0838 (*M*+H calcd for C₂₂H₂₁BrF₂N₂O₄ requires 463.0827).

Example 209

4-[(2,4-difluorobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2-(1H)-one.
30



Step 1. Preparation of 1-(4-methoxybenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one.



5

4-Hydroxy-6-methyl-2-pyrone (4.60 g, 36.45 mmol) and 4-methoxybenzylamine (5.00 g, 36.45 mmol) in H₂O (100 mL) were heated to reflux. After 15 hours at reflux the reaction was allowed to cool to room temperature. The precipitate was collected by filtration washing with H₂O to give a pale yellow solid (8.00 g, 89 %). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.2 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.74 (d, *J* = 2.0 Hz, 1H), 5.56 (d, *J* = 2.5 Hz, 1H), 5.08 (s, 2H), 3.68 (s, 3H), 2.14 (s, 3H).

15

Step 2. Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one. 1-(4-methoxybenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one (Step 1) (7.97 g, 32.49 mmol) was dissolved in *N,N*-dimethylformamide (60 mL). Potassium carbonate (4.94 g, 35.74 mmol) was added, followed by α-bromo-2,4-difluorotoluene (4.38 mL, 34.11 mmol). The reaction was stirred at room temperature for 20 hours at which time the mixture was filtered through a pad of Celite®

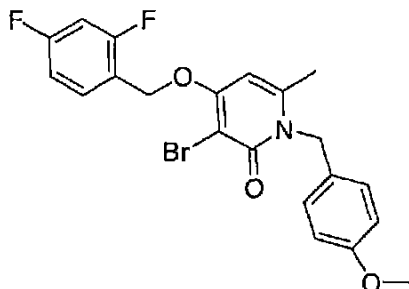
20

washing with acetonitrile and the filtrate was evaporated. The residue was dissolved in H₂O (150 mL) and extracted into ethyl acetate (2 x 100 mL). The organic phase was washed with brine (100 mL), dried over Na₂SO₄, filtered and evaporated.

5 Chromatography (on silica, hexanes/ethyl acetate with 10% methanol) yielded an off-white solid (3.64 g, 30%). ¹H NMR (300 MHz CDCl₃) δ 7.42 (*app* q, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.96-6.84 (m 2H), 6.85 (*app* d, *J* = 8.7 Hz, 2H), 6.01 (d, *J* = 2.6 Hz, 1H), 5.82 (d, *J* = 2.8 Hz, 1H), 5.23 (s, 2H), 5.02 (s, 2H), 3.79 (s, 3H), 2.25 (s, 3H). ES-HRMS *m/z* 372.1412 (*M*+H C₂₁H₁₉F₂NO₃ requires 372.1417).

Example 210

15 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one



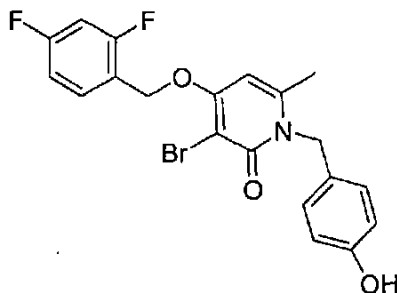
Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(4-methoxybenzyl)-6-methylpyridin-2(1H)-one. EXAMPLE 209 (0.200 g, 0.538 mmol) suspended in acetonitrile (3 mL) was cooled in an ice-bath. *N*-bromosuccinimide (0.101 g, 0.565 mmol) was added. Once the addition was complete the cooling bath was removed. After 1 hour the reaction was concentrated.

25 Purification by chromatography (silica gel, hexanes/ethyl acetate) provided a white solid (0.240 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 7.59 (*app* q, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.97 (*app* dt, *J* = 2.4, 8.6 Hz, 1H), 6.91-6.83 (m,

1H), 6.85 (*app* d, $J = 8.7$ Hz, 2H), 5.98 (s, 1H), 5.31 (s, 2H), 5.21 (s, 2H), 3.79 (s, 3H), 2.34 (s, 3H). ES-HRMS m/z 450.0491 ($M+H$ $C_{21}H_{18}BrF_2NO_3$ requires 450.0511).

5 Example 211

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(4-hydroxybenzyl)-6-methylpyridin-2(1H)-one



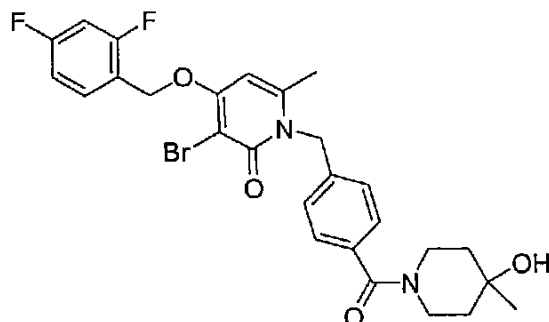
10

Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(4-hydroxybenzyl)-6-methylpyridin-2(1H)-one. EXAMPLE 210 (0.235 g, 0.522 mmol) was suspended in acetonitrile (3 mL). Ceric ammonium nitrate (1.14 g, 2.09 mmol) dissolved in H_2O (1 mL) was added. The reaction was stirred at room temperature for 1 hour and then diluted with dichloromethane (25 mL). The reaction was then washed with H_2O (10 mL). The aqueous phase was back extracted with dichloromethane (20 mL). The combined organic layers were dried over Na_2SO_4 , filtered and evaporated. The residue was washed with hot ethyl acetate to give an off-white solid (0.134 g, 59%). 1H NMR (300 MHz, $DMSO-d_6$) δ 7.75 (*app* q, $J = 7.9$ Hz, 1H), 7.65 (s, 1H), 7.45-7.36 (m, 1H), 7.36 (d, $J = 10.1$ Hz, 2H), 7.27-7.20 (m, 1H), 6.49 (d, $J = 10.1$ Hz, 2H), 5.60 (s, 2H), 5.07 (s, 2H), 2.63 (s, 3H). ES-HRMS m/z 436.0187 ($M+H$ $C_{20}H_{16}BrF_2NO_3$ requires 436.0354).

Example 212

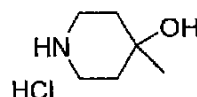
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one.

5



Step 1. Preparation of 4-hydroxy-4-methylpiperidine hydrochloride.

10



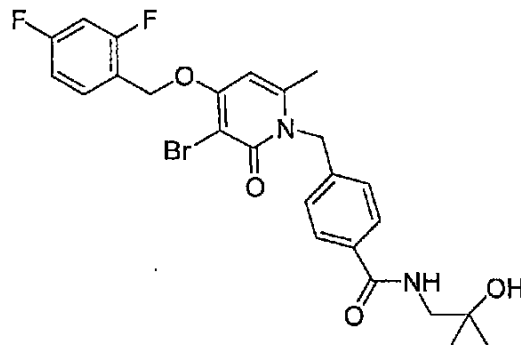
tert-Butyl-4-oxo-1-piperidine (10.0 g, 50.19 mmol) dissolved in diethyl ether (100 mL) was cooled in an ice-bath. Methyl magnesium bromide (18.40 mL, 55.21 mmol, 3.0 M in diethyl ether) was added. After slowly warming to room temperature the reaction was recooled in an ice-bath and quenched by the addition of saturated NH_4Cl (75 mL). Additional H_2O was added and the organic layer was removed. The aqueous layer was further extracted with diethyl ether (50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated. Chromatography (silica gel, hexanes/ethyl acetate) provided a clear oil. The resulting oil was dissolved in diethyl ether (10 mL) and treated with 4N HCl/dioxane (32.61 mL, 130.43 mmol). After stirring at room temperature for 1 hour the reaction mixture was concentrated to give a pale yellow solid (5.05 g, >100%).

25

Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1{4-[(4-hydroxy-4-methylpiperidin-1-yl)carbonyl]benzyl}-6-methylpyridin-2(1H)-one. THE ACID (0.300 g, 0.646 mmol) was
5 suspended in dichloromethane (6.0 mL). 1-hydroxybenzotriazole (0.044 g, 0.323 mmol) was added followed by 3-(1-cyclohexylcarbodiimide)propyl-functionalized silica gel (2.02 g, 1.29 mmol, loading = 0.64 mmol/g), 3-(1-morpholine)propyl functionalized silica gel (1.84 g, 1.29 mmol, loading = 0.7
10 mmol/g) and dichloromethane (2 mL). After stirring at room temperature for 15 minutes, 4-hydroxy-4-methylpiperidine hydrochloride (0.147 g, 0.969 mmol) was added. The resulting mixture was stirred at room temperature overnight, at which time dimethylamine-3-functionalized silica gel (1.7 g, 2.58
15 mmol, loading = 1.5 mmol/g) was added followed by isocyanate-3-functionalized silica gel (1.3 g, 1.62 mmol, loading = 1.22 mmol/g). The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was then filtered and concentrated. Chromatography (silica gel,
20 hexanes/ethyl acetate with 10% methanol) provided a white foam (0.200 g, 55%). ¹H NMR (300 MHz, CDCl₃) δ 7.58 (app q, J = 7.7 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 6.96 (app t, J = 8.3 Hz, 1H), 6.87 (app dt, J = 2.0, 9.5 Hz, 1H), 6.06 (s, 1H), 5.38 (s, 2H), 5.22 (s, 2H), 4.27 (br m,
25 1H), 3.41 (br m, 3H), 2.30 (s, 3H), 2.06 (s, 1H), 1.60 (br m, 4H), 1.28 (s, 3H). ES-HRMS m/z 561.1173 (M+H C₂₇H₂₇BrF₂N₂O₄ requires 561.1195).

30 Example 213

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxypyridin-1(2H)-yl]methyl}-N-(2-hydroxy-2-methylpropyl)benzamide.



5

The title compound was by a procedure essentially as in Example 212 using 1-amino-2-methyl-2-propanol hydrochloride as starting material.

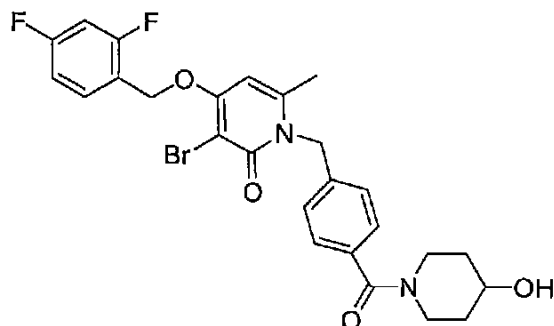
10

^1H NMR (400 MHz, CDCl_3) δ 7.70 (d, $J = 8.3$ Hz, 2H), 7.53 (app q, $J = 7.8$ Hz, 1H), 7.33 (t, $J = 5.8$ Hz, 1H), 7.06 (d, $J = 8.3$ Hz, 2H), 6.95-6.90 (m, 1H), 6.86-6.81 (m, 1H), 6.04 (s, 1H), 5.30 (s, 2H), 5.19 (s, 2H), 3.40 (d, $J = 5.9$ Hz, 2H), 2.98 (br s, 1H), 2.24 (s, 3H), 1.21 (s, 6H). ES-HRMS m/z 535.1012 ($M+H$ $\text{C}_{25}\text{H}_{25}\text{BrF}_2\text{N}_2\text{O}_4$ requires 535.1039).

15

Example 214

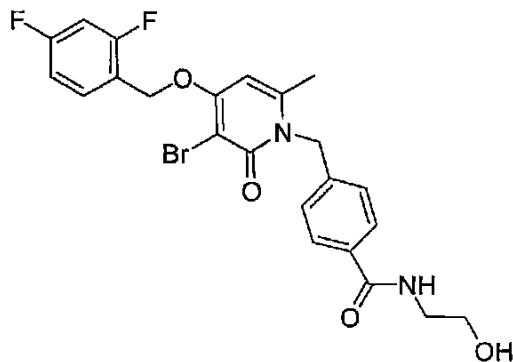
20 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-[(4-hydroxypiperidin-1-yl)carbonyl]benzyl]-6-methylpyridin-2(1H)-one.



The title compound was produced essentially as in Example 212 using 4-hydroxypiperidine as starting material. ¹H NMR (400
 5 MHz, CDCl₃) δ 7.55 (*app* q, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.94 (*app* dt, *J* = 2.4, 8.4 Hz, 1H), 6.84 (*app* ddd, *J* = 2.6, 8.9, 10.3 Hz, 1H), 6.01 (s, 1H), 5.36 (s, 2H), 5.19 (s, 2H), 4.12-4.07 (m, 1H), 3.96-3.90 (m, 1H), 3.60 (*br* s, 1H), 3.33 (*br* s, 1H), 3.13 (*br* s, 1H),
 10 2.27 (s, 3H), 1.91 (*br* s, 3H), 1.77 (*br* s, 1H), 1.57 (*br* s, 1H), 1.44 (*br* s, 1H). ES-HRMS *m/z* 547.1006 (M+H C₂₆H₂₅BrF₂N₂O₄ requires 547.1039).

Example 215

4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzamide.

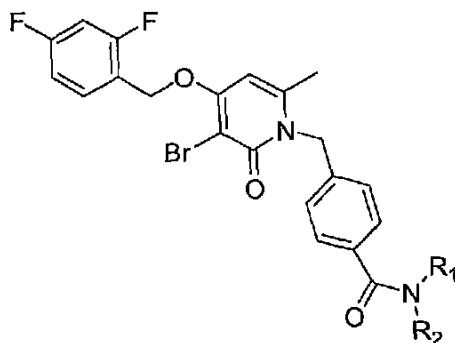


Preparation of 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)benzamide. To a reaction vessel (borosilicate culture tube) was added EXAMPLE 205 (0.300 g, 0.646 mmol). A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M) was added to the reaction vessel followed by approximately 1.10 g of the polymer bound carbodiimide resin (1.8 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. Ethanolamine (0.06 mL, 0.994 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 2.6 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed further with tetrahydrofuran (2 x 10 mL) and combined with the partially reduced filtrate. The resulting filtrate was concentrated by blowing N₂ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid. (0.111 g, 34%) ¹H NMR (400 MHz, DMF-d₆) δ 8.45 (t, *J* = 5.4 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.76 (app q, *J* = 7.9 Hz, 1H), 7.33-7.27 (m, 1H), 7.27 (app d, *J* = 7.9 Hz, 2H), 7.20 (app dt, *J* = 2.4, 8.6 Hz, 1H), 6.65 (s, 1H), 5.47 (s, 2H), 5.38 (s, 2H), 4.83 (br s, 1H),

3.64-3.60 (m, 2H), 2.47-3.42 (m, 2H), 2.40 (s, 3H). ES-HRMS
m/z 507.0742 (M+H C₂₃H₂₁BrF₂N₂O₄ requires 507.0726).

Example 216-231

- 5 Preparation of 3-bromo-4-(2,4-difluorophenoxy)-6-methyl-1-[4-(aminocarbonyl)benzyl]pyridin-2(1H)-one compounds



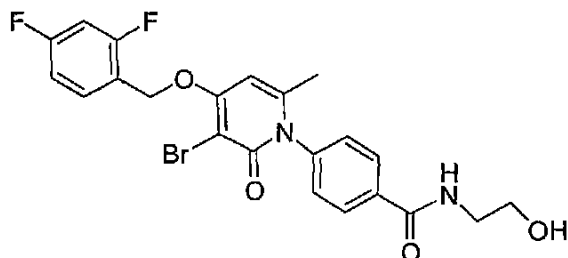
- 10 By following the method of Example 215 and substituting the appropriate amine, the compounds of Examples 216-231 are prepared. The deprotection of the protected intermediates was accomplished with 4N HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R ₁	R ₂	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 216	CH ₂ CH ₂ NH-	CH ₂ CH ₂ NH-	73	C ₂₅ H ₂₄ BrF ₂ N ₃ O ₄	532.1042	532.102
Ex. 217	H	CH ₂ CH ₂ NH ₂	49	C ₂₃ H ₂₂ BrF ₂ N ₃ O ₃	506.0885	506.088
Ex. 218	H	CH ₂ CH ₂ CH ₂ NH ₂	31	C ₂₄ H ₂₄ BrF ₂ N ₃ O ₃	520.1042	520.104
Ex. 219	H	OH	53	C ₂₁ H ₁₇ BrF ₂ N ₂ O ₄	479.0413	479.042
Ex. 220	H	CH ₃	59	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₄	477.0620	477.060
Ex. 221	CH ₃	CH ₃	51	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₃	491.0776	491.079
Ex. 222	CH ₂ CH ₂ O-	CH ₂ CH ₂ O-	61	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₄	533.0882	533.090
Ex. 223	CH ₂ CH ₂ OH	CH ₂ CH ₂ OH	69	C ₂₅ H ₂₅ BrF ₂ N ₂ O ₅	551.0988	551.097
Ex. 224	CH ₂ CH ₂ CH ₂ -	CH ₂ CH ₂ CH ₂ -	66	C ₂₆ H ₂₅ BrF ₂ N ₂ O ₃	531.1084	531.108
Ex. 225	H	CH(CH ₃) ₂	50	C ₂₄ H ₂₃ BrF ₂ N ₂ O ₃	505.0933	505.090

Ex. 226	CH ₂ CH ₂ -	CH ₂ CH ₂ -	71	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₃	517.0933	517.0908
Ex. 227	CH ₂ CH ₂ N(CH ₃) -	CH ₂ CH ₂ N(CH ₃) -	83	C ₂₆ H ₂₆ BrF ₂ N ₃ O ₃	546.1198	546.1215
Ex. 228	H	CH ₂ CH ₂ N(CH ₃) ₂	81	C ₂₅ H ₂₆ BrF ₂ N ₃ O ₃	534.1198	534.1197
Ex. 229	H	CH ₂ CH ₂ OCH ₃	79	C ₂₄ H ₂₃ BrF ₂ N ₂ O ₄	521.0882	521.0861
Ex. 230	CH ₃	CH ₂ CH ₂ OH	36	C ₂₄ H ₂₃ BrF ₂ N ₂ O ₄	521.0882	521.0893
Ex. 231	CH ₃	CH ₂ CH ₂ OCH ₃	82	C ₂₅ H ₂₅ BrF ₂ N ₂ O ₄	535.1039	535.1028

Example 232

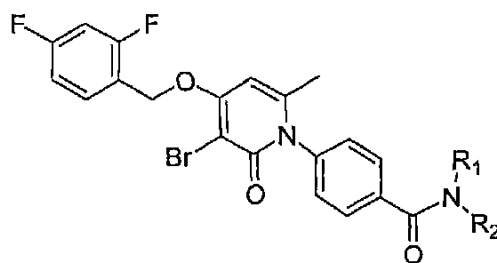
4-{ [3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-
 5 1(2H)-yl] - N-(2-hydroxyethyl)benzamide.



Preparation of 4-{ [3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl] - N-(2-hydroxyethyl)benzamide. To
 10 a reaction vessel (borosilicate culture tube) was added
 EXAMPLE 203 (0.300 g, 0.666 mmol). A stock solution of 1-
 hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M)
 was added to the reaction vessel followed by approximately
 1.13 g of the polymer bound carbodiimide resin (1.8 mmol/g).
 15 Additional *N,N*-dimethylformamide (2 mL) was then added to the
 reaction vessel. The parallel reaction apparatus was then
 orbitally shaken (Labline Benchtop Orbital Shaker) at
 approximately 200 RPM at room temperature for 15 minutes.
 Ethanolamine (0.06 mL, 0.994 mmol) was then added to the
 20 reaction vessel and the reaction apparatus was orbitally
 shaken at room temperature overnight. At this time the
 reaction was diluted with tetrahydrofuran (20 mL) and treated

with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 2.7 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed further with tetrahydrofuran (2 x 10 mL) and combined with the partially reduced filtrate. The resulting filtrate was concentrated by blowing N₂ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor). Purification by chromatography (silica gel) provided an off-white solid (0.155 g, 47%). ¹H NMR (400 MHz, DMF-d₆) δ 8.58 (t, J = 5.5 Hz, 1H), 8.10 (d, J = 8.3 Hz, 2H), 7.79 (app q, J = 7.9 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.36-7.30 (m, 1H), 7.21 (app dt, J = 2.4, 8.5 Hz, 1H), 6.73 (s, 1H), 5.43 (s, 2H), 3.68 (app t, J = 5.9 Hz, 2H), 3.52-3.49 (m, 2H), 2.03 (s, 3H). ES-HRMS m/z 493.0597 (M+H C₂₂H₁₉BrF₂N₂O₄ requires 493.0569).

Examples 233-243

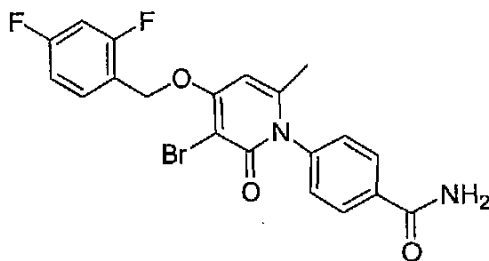


By following the method of Example 232 and substituting ethanolamine for the appropriate amine, the compounds of Examples 233-243 are prepared. The deprotection of the protected intermediates was accomplished with 4N HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R ₁	R ₂	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 233	CH ₂ CH ₂ NH-	CH ₂ CH ₂ NH-	40.3	C ₂₄ H ₂₂ BrF ₂ N ₃ O ₃	518.0885	518.0866
Ex. 234	H	CH ₂ CH ₂ NH ₂	57.1	C ₂₂ H ₂₀ BrF ₂ N ₃ O ₃	492.0729	492.0748
Ex. 235	H	CH ₂ CH ₂ CH ₂ NH ₂	21.5	C ₂₃ H ₂₂ BrF ₂ N ₃ O ₃	506.0885	506.0915
Ex. 236	H	OH	33.9	C ₂₀ H ₁₅ BrF ₂ N ₂ O ₄	465.0256	465.0259
Ex. 237	H	CH ₃	20.7	C ₂₁ H ₁₇ BrF ₂ N ₂ O ₃	463.0463	463.0479
Ex. 238	CH ₃	CH ₃	22.3	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₃	477.0620	477.0643
Ex. 239	CH ₂ CH ₂ O-	CH ₂ CH ₂ O-	84.4	C ₂₄ H ₂₁ BrF ₂ N ₂ O ₄	519.0726	519.0723
Ex. 240	CH ₂ CH ₂ OH	CH ₂ CH ₂ OH	46.6	C ₂₄ H ₂₃ BrF ₂ N ₂ O ₅	537.0831	537.0854
Ex. 241	CH ₂ CH ₂ CH ₂ -	CH ₂ CH ₂ CH ₂ -	76.5	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₃	517.0933	517.0892
Ex. 242	H	CH(CH ₃) ₂	52.6	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₃	491.0776	491.0781
Ex. 243	CH ₂ CH ₂ -	CH ₂ CH ₂ -	47.2	C ₂₄ H ₂₁ BrF ₂ N ₂ O ₄	503.0776	503.0791

Ex. 244

4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide.



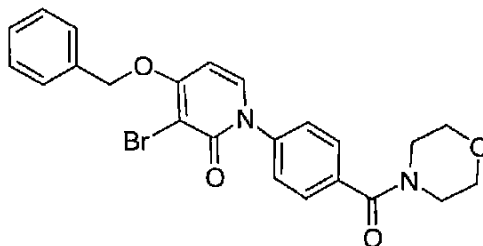
Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide. EXAMPLE 203 (0.500 g, 1.11 mmol) was suspended in tetrahydrofuran (5.0 mL). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0.234 g, 1.33 mmol) was added followed by 4-methylmorpholine (0.366 mL, 3.33 mmol). The resulting mixture was stirred at room temperature for 1.5

hours at which time NH_4OH (2.5 mL) was added. The resulting mixture was stirred at room temperature overnight. H_2O (25 mL) and tetrahydrofuran (25 mL) was added. The aqueous layer was further extracted with ethyl acetate (25 mL). The combined
5 organic layers were washed with saturated sodium carbonate solution (25 mL), 1N HCl (25 mL), brine (25 mL), dried over Na_2SO_4 , filtered and concentrated to provide a pale yellow solid (0.500 g, 100 %). ^1H NMR (400 MHz, DMF-d_6) δ 8.13 (s, 1H), 8.02 (d, $J = 8.5$ Hz, 2H), 7.70 (app q, $J = 7.9$ Hz, 1H),
10 7.40 (d, $J = 8.5$ Hz, 2H), 7.41-7.34 (m, 1H), 7.22 (app dt, $J = 1.8, 8.5$ Hz, 1H), 6.71 (s, 1H), 5.37 (s, 2H), 1.97 (s, 3H). ES-HRMS m/z 449.0281 ($\text{M}+\text{H}$ $\text{C}_{20}\text{H}_{15}\text{BrF}_2\text{N}_2\text{O}_3$ requires 449.0307).

Ex. 245

15

4-(Benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1H)-one.



20

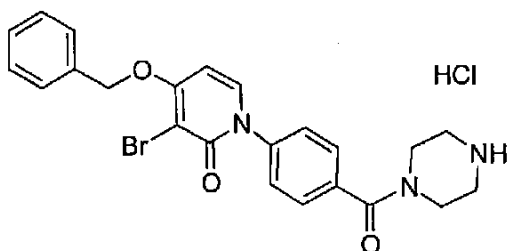
Preparation of 4-(Benzyloxy)-3-bromo-1-[4-(morpholin-4-ylcarbonyl)phenyl]pyridin-2(1H)-one. To a reaction vessel (borosilicate culture tube) was added EXAMPLE 197 (0.100 g, 0.250 mmol) which was dissolved in *N,N*-dimethylformamide (2.0
25 mL). 1-Hydroxybenzotriazole (0.017 g, 0.125 mmol) was added to the reaction vessel followed by approximately 0.423 g of the polymer bound carbodiimide resin (1.8 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction

vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. Morpholine (0.033 g, 0.0.375 mmol) dissolved in *N,N*-dimethylformamide (0.5 mL) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with *N,N*-dimethylformamide (2.0 mL) and dichloromethane (4.0 mL) and treated with approximately 0.770 g of polyamine resin (2.63 mmol/g) and approximately 1.0 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 10 mL). The filtrate was evaporated by blowing N₂ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid (0.092 g, 79%).

¹H NMR (400 MHz, CDCl₃) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.48-7.33 (m, 7H), 7.27 (d, *J* = 7.8 Hz, 1H), 6.19 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 2H), 3.76-3.47 (br m, 8H). ES-HRMS *m/z* 469.0733 (M+H C₂₃H₂₁BrN₂O₄ requires 469.0757).

Ex. 246

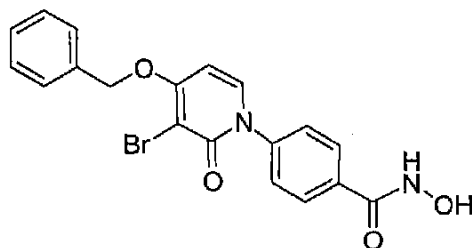
4-(Benzyloxy)-3-bromo-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1H)-one hydrochloride.



Preparation of 4-(benzyloxy)-3-bromo-1-[4-(piperazin-1-ylcarbonyl)phenyl]pyridin-2(1H)-one hydrochloride. By
 5 following the method of Ex. 245 and substituting *N*-tert-butyl carboxylate piperazine (0.070 g, 0.375 mmol) for morpholine the title compound was prepared as the *N*-t-butoxycarbonyl protected compound. The deprotection of the *N*-t-butoxycarbonyl intermediate was accomplished with 4*N* HCl in
 10 dioxane to afford the title compound as its hydrochloride salt (0.112 g, >100%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.55 (*br s*, 2H), 7.78 (*d*, *J* = 7.8 Hz, 1H), 7.58 (*d*, *J* = 8.5 Hz, 2H), 7.48-7.33 (*m*, 7H), 6.57 (*d*, *J* = 7.8 Hz, 1H), 5.38 (*s*, 2H), 3.79-3.36 (*br m*, 4H), 3.30-3.14 (*br s*, 4H). ES-HRMS *m/z* 468.0940 (*M*+H
 15 C₂₃H₂₂BrN₃O₃ requires 468.0917).

Ex. 247

4-[4-(Benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]-*N*-
 20 hydroxybenzamide.

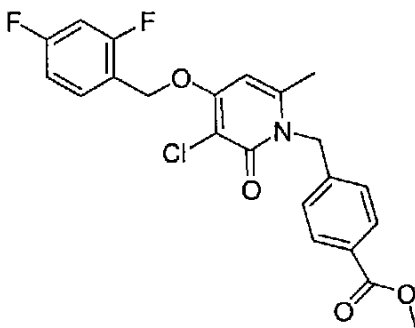


Preparation of 4-[4-(Benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]-*N*-hydroxybenzamide. By following the method of EXAMPLE 245

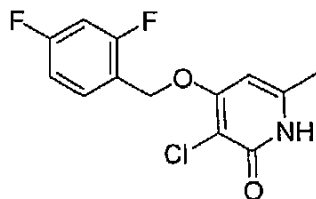
and substituting O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.044 g, 0.375 mmol) for morpholine the title compound was prepared as the tetrahydropyranly protected compound. The deprotection of the tetrahydropyranly intermediate was accomplished with 4N HCl in dioxane to afford the title compound (0.056 g, >71%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.03 (br s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 7.8 Hz, 1H), 7.48-7.35 (m, 7H), 6.55 (d, J = 7.8 Hz, 1H), 5.37 (s, 2H). ES-HRMS m/z 415.0278 (M+H C₁₉H₁₅BrN₂O₄ requires 415.0288).

Ex. 248

Methyl-4-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzoate.



Step 1. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.

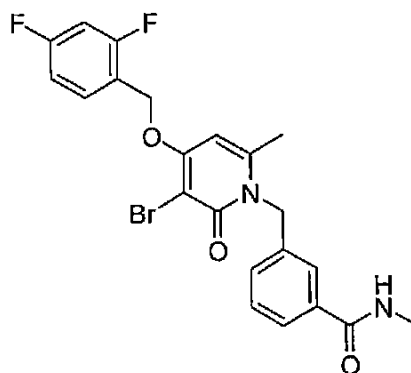


(5.00 g, 19.90 mmol) was suspended in 1,2-dichloroethane (100 mL). Dichloroacetic acid (0.082 mL, 0.995 mmol) was added, followed by N-chlorosuccinimide (3.19 g, 23.88 mmol). The reaction mixture was heated at 80 °C for 15.5 hours. The 1,2-

dichloroethane was evaporated and the remaining solids were washed with acetonitrile to provide a tan solid (4.97 g, 88%).

Step 2. Preparation of methyl-4-([3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl)methyl}benzoate. 3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (Step 1) (4.97 g, 17.40 mmol) suspended in tetrahydrofuran (50 mL) was cooled in an ice-bath. Methyl 4-(bromomethyl)benzoate (5.98 g, 26.10 mmol) was added, followed by sodium hydride (0.835 g, 20.88 mmol, 60% dispersion in mineral oil). Once the addition was complete the cooling bath was removed in the mixture was heated to 50 °C for 19 hours. After cooling to room temperature saturated NH₄Cl (50 mL) was added. Ethyl acetate was added and the precipitate was collected by filtration. The filtrate was further extracted with ethyl acetate. The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and evaporated. The resulting solid was combined with the precipitate and washed with hot ethyl acetate to give an off-white solid (5.24 g, 69%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.90 (d, J = 8.5 Hz, 2H), 7.63 (app q, J = 7.9 Hz, 1H), 7.31 (app dt, J = 2.4, 9.9 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 7.17-7.13 (m, 1H), 6.60 (s, 1H), 5.36 (s, 2H), 5.27 (s, 2H), 3.81 (s, 3H), 2.27 (s, 3H). ES-HRMS m/z 434.0931 (M+H C₂₂H₁₈BrF₂NO₄ requires 434.0965).

Example 249



3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-methylbenzamide

5

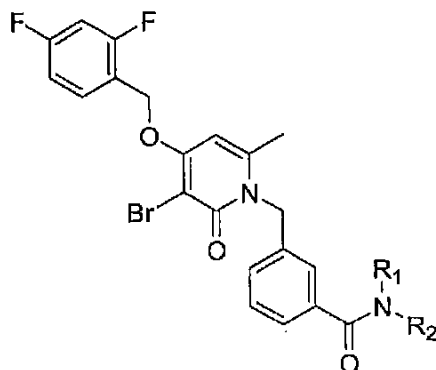
To a reaction vessel (borosilicate culture tube) was added EXAMPLE 169 (0.300 g, 0.646 mmol). A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M) was added followed by approximately 1.10 g of the polymer bound carbodiimide resin (1.8 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. *N*-Methylamine (0.50 mL, 0.999 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (35 mL) and treated with approximately 2.0 g of polyamine resin (2.63 mmol/g) and approximately 2.6 g of methylisocyanate functionalized polystyrene (1.50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The

25

filtrate was evaporated by blowing N₂ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor). Chromatography (C-18, acetonitrile/H₂O with 0.1% trifluoroacetic acid) afforded a white solid (0.178 g, 58%).

5 ¹H NMR (400 MHz, DMF-d₆) δ 7.65-7.53 (m, 3H), 7.37-7.28 (m, 2H), 6.97-6.82 (m, 2H), 6.00 (s, 1H), 5.36 (s, 2H), 5.19 (s, 3H), 2.96 (t, J = 4.83 Hz, 3H), 2.29 (s, 3H). ES-HRMS m/z 477.0635 (M+H C₂₂H₁₉BrF₂N₂O₃ requires 477.0620).

10 Preparation of Examples 250- 261

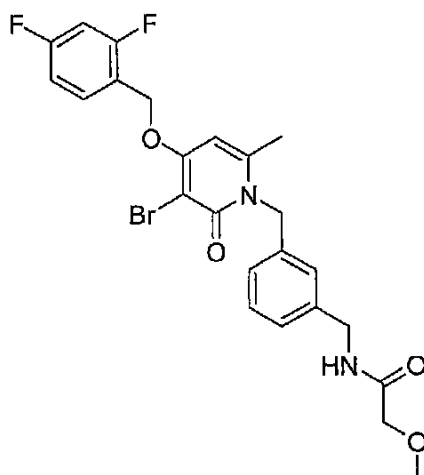


By following the method of Example 249 and replacing N-methylamine with the appropriate amine, the compounds of Examples 250-261 are prepared. The deprotection of the
15 protected intermediates was accomplished with 4N HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R ₁	R ₂	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 250	CH ₂ CH ₂ NH-	CH ₂ CH ₂ NH-	89	C ₂₅ H ₂₄ BrF ₂ N ₃ O ₄	532.1042	532.1067
Ex. 251	H	CH ₂ CH ₂ NH ₂	75	C ₂₃ H ₂₂ BrF ₂ N ₃ O ₃	506.0885	506.0900
Ex. 252	H	CH ₂ CH ₂ CH ₂ NH ₂	84	C ₂₄ H ₂₄ BrF ₂ N ₃ O ₃	520.1042	520.1000
Ex. 253	H	OH	45	C ₂₁ H ₁₇ BrF ₂ N ₂ O ₄	479.0413	479.0394
Ex. 254	CH ₃	CH ₃	69	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₃	491.0776	491.0731

Ex. 255	H	CH ₃	58	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₃	479.0602	479.0598
Ex. 256	CH ₂ CH ₂ O-	CH ₂ CH ₂ O-	69	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₄	533.0882	533.0857
Ex. 257	H	CH ₂ CH ₂ OH	51	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₄	507.0726	507.0698
Ex. 258	CH ₂ CH ₂ OH	CH ₂ CH ₂ OH	25	C ₂₅ H ₂₅ BrF ₂ N ₂ O ₅	551.0988	551.0972
Ex. 259	CH ₂ CH ₂ CH ₂ -	CH ₂ CH ₂ CH ₂ -	62	C ₂₆ H ₂₅ BrF ₂ N ₂ O ₃	531.1089	531.1088
Ex. 260	H	CH(CH ₃) ₂	46	C ₂₄ H ₂₃ BrF ₂ N ₂ O ₃	505.0933	505.0918
Ex. 261	CH ₂ CH ₂ -	CH ₂ CH ₂ -	60	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₃	517.0933	517.0950

Example 262

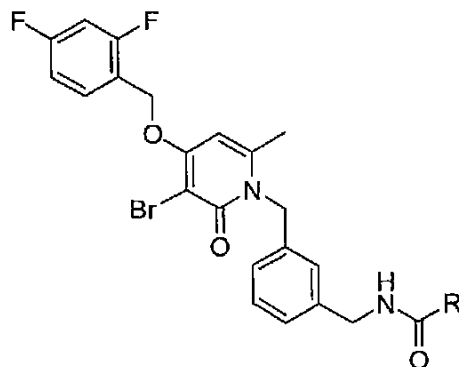


5 N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-methoxyacetamide

To a reaction vessel (borosilicate culture tube) was added methoxyacetic acid (0.09 g, 1.00 mmol). A stock solution of
 10 1-hydroxybenzotriazole (3 mL, 0.16 M) and *N*-methylmorpholine (3 mL, 0.43 M) in *N,N*-dimethylformamide were added to the reaction vessel followed by approximately 0.97 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional
 15 *N,N*-dimethylformamide (3 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 4 hours. 1-[3-

(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (0.30 g, 0.668 mmol) was then added to the reaction vessel followed by additional *N,N*-dimethylformamide (5.0 mL) and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2.06 g of polyamine resin (2.63 mmol/g) and approximately 2.67 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N₂ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) afforded a tan solid (0.321 g, 89.4%). ¹H NMR (400 MHz, DMF-d₆) δ 8.33 (br s, 1H), 7.81 (app q, *J* = 7.85 Hz, 1H), 7.40-7.23 (m, 5H), 7.09 (d, *J* = 7.25 Hz, 1H), 6.68 (s, 1H), 5.46 (s, 2H), 5.42 (s, 2H), 4.45 (d, *J* = 6.24 Hz, 2H), 3.93 (s, 2H), 3.39 (s, 3H), 2.44 (s, 3H). ES-HRMS *m/z* 521.0891 (M+H C₂₄H₂₃BrF₂N₂O₄ requires 521.0882).

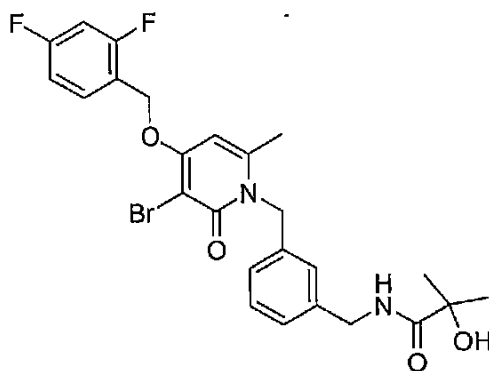
Preparation of Example 263-265



By following the method of Example 262 and replacing methoxyacetic acid with the appropriate acid, the compounds of Examples 263-265 are prepared. The deprotection of the
 5 protected intermediates was accomplished with 4N HCl in dioxane to afford the compounds as hydrochloride salts.

Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 263	CH ₂ NH ₂	46.1	C ₂₃ H ₂₃ BrF ₂ N ₃ O ₃	506.0885	506.0870
Ex. 264	CH ₂ NHCOCH ₃	70.4	C ₂₅ H ₂₄ BrF ₂ N ₃ O ₄	548.0991	548.1007
Ex. 265	CH ₂ OCOCH ₃	42.7	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₄	549.0831	549.0837

Example 266



10

N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-2-hydroxy-2-methylpropanamide

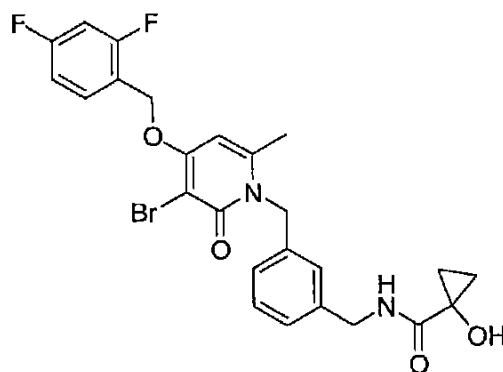
15

1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (0.300 g, 0.668 mmol), 1-hydroxyisobutyric acid (0.215 g, 2.064 mmol), 1-hydroxybenzotriazole (0.112 g, 0.826 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.185
 20 g, 0.963 mmol) were dissolved in N,N-dimethylacetamide (3 mL).

N-methylmorpholine (0.209 g, 2.064 mmol) was added, and the reaction stirred for 1 hour at room temperature. The reaction was diluted with H₂O (50 mL) and the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organics were
 5 then washed with 1N HCl (25 mL), saturated Na₂CO₃ (25 mL), brine (25 mL), dried over Na₂SO₄, and concentrated to yield an off-white solid (0.235 g, 64%). ¹H NMR (400 MHz, DMF-d₆) δ 8.25 (br s, 1H), 7.81 (app q, *J* = 7.92 Hz, 1H), 7.40-7.21 (m, 5H), 7.09 (d, *J* = 6.84 Hz, 1H), 6.67 (s, 1H), 5.46 (s, 2H),
 10 5.42 (s, 2H), 4.42 (d, *J* = 6.24 Hz, 2H), 2.44 (s, 3H), 1.38 (s, 6H). ES-HRMS *m/z* 535.1024 (M+H C₂₅H₂₅BrF₂N₂O₄ requires 535.1039).

Example 267

15

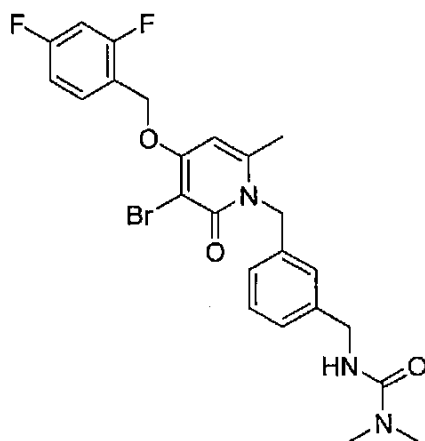


N-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-1-hydroxycyclopropanecarboxamide
 20

By following the method of Example 266 and substituting 1-hydroxy-1-cyclopropane-carboxylic acid for 1-hydroxyisobutyric
 25 acid, the title compound was prepared (0.352 g, 96%). ¹H NMR (400 MHz, DMF-d₆) δ 8.46 (app t, *J* = 6.24 Hz, 1H), 7.81 (app q,

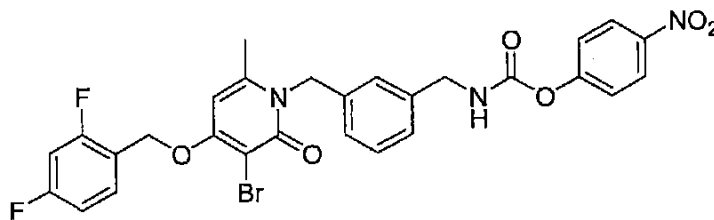
$J = 7.92$ Hz, 1H), 7.40-7.22 (m, 5H), 7.06 (d, $J = 7.05$ Hz, 1H), 6.67 (s, 1H), 5.45 (s, 2H), 5.42 (s, 2H), 4.46 (d, $J = 6.44$ Hz, 2H), 2.45 (s, 3H), 1.17-1.12 (m, 2H), 0.93 (app q, $J = 3.82$ Hz, 2H). ES-HRMS m/z 533.0861 (M+H $C_{25}H_{23}BrF_2N_2O_4$ requires 533.0882).

Example 267



N'-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea

Step 1: Preparation of 4-nitrophenyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzylcarbamate.



1-[3-(aminomethyl)benzyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (EXAMPLE 161) (2.00 g, 4.45 mmol)

was suspended in dichloromethane (15 mL). Pyridine was added (0.43 mL, 5.34 mmol). After stirring for 10 minutes at room temperature, a stock solution of 4-nitrophenyl chloroformate (10.0 mL, 0.50 M) in dichloromethane was added dropwise.

5 After stirring for 4.5 hours at room temperature, a stock solution of 4-nitrophenyl chloroformate (2.5 mL, 0.50 M) in dichloromethane was again added dropwise and stirring continued at 40 °C overnight. The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a yellow

10 solid (1.11 g, 66%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (*app* t, *J* = 6.10 Hz, 1H), 8.24-8.21 (m, 2H), 7.62 (*app* q, *J* = 7.88 Hz, 1H), 7.40-7.27 (m, 7H), 6.98 (d, *J* = 7.52 Hz, 1H), 6.54 (s, 1H), 5.30 (s, 2H), 5.24 (s, 2H), 4.25 (d, *J* = 6.18 Hz, 2H),

15 2.30 (s, 3H). ES-HRMS *m/z* 614.0753 (M+H C₂₈H₂₂BrF₂N₃O₆ requires 614.0733).

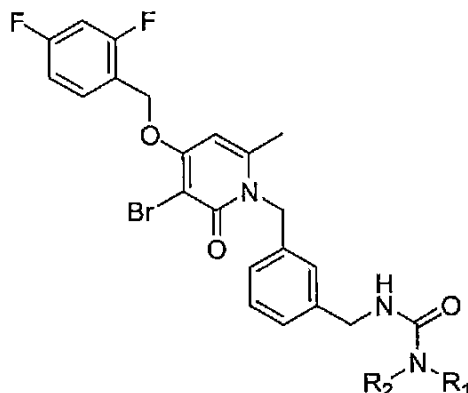
Step 2: Preparation of N'-(3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzyl)-N,N-dimethylurea . To a reaction vessel (borosilicate culture tube) was added 4-nitrophenyl 3-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzylcarbamate (from step 1) (0.350 g, 0.570 mmol) dissolved in dichloromethane (6.0 mL). The parallel reaction

25 apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. A stock solution of N,N-dimethylamine in tetrahydrofuran (0.427 mL, 2.0 M) was then added to the reaction vessel and the reaction apparatus was orbitally

30 shaken at room temperature overnight. The reaction mixture was concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off

white solid (0.226 g, 63.3%). ^1H NMR (400 MHz, DMF-d_6) δ 7.81 (app q, $J = 7.92$ Hz, 1H), 7.40-7.19 (m, 5H); 7.06 (d, $J = 7.45$ Hz, 1H), 6.88 (app t, $J = 5.84$ Hz, 1H), 6.68 (s, 1H), 5.45 (s, 2H), 5.42 (s, 1H), 4.35 (d, $J = 5.84$ Hz, 1H), 2.92 (s, 6H),
 5 2.44 (s, 3H). ES-HRMS m/z 520.1065 ($\text{M}+\text{H}$ $\text{C}_{24}\text{H}_{24}\text{BrF}_2\text{N}_3\text{O}_3$ requires 520.1042).

Preparation of Example 268-270



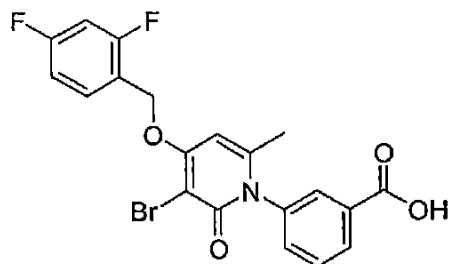
10

By following the method of Example 267 and replacing *N,N*-dimethylamine with the appropriate amine, the compounds of Examples 268-270 are prepared. The deprotection of the protected intermediates was accomplished with 4*N* HCl in
 15 dioxane to afford the compounds as hydrochloride salts.

Compound No.	R_1	R_2	% Yield	MF	$\text{M}+\text{H}$ Requires	ES-HRMS m/z
Ex. 268	$\text{CH}_2\text{CH}_2\text{N}-\text{CH}_2\text{CH}_2\text{N}-$		66.6	$\text{C}_{26}\text{H}_{27}\text{BrF}_2\text{N}_4\text{O}_3$	561.1307	561.1309
Ex. 269	H	CH_3	27.0	$\text{C}_{23}\text{H}_{22}\text{BrF}_2\text{N}_3\text{O}_3$	506.0885	506.0898
Ex. 270	$\text{CH}_2\text{CH}_2\text{O}-\text{CH}_2\text{CH}_2\text{O}-$		64.4	$\text{C}_{26}\text{H}_{26}\text{BrF}_2\text{N}_3\text{O}_4$	562.1148	562.1137

Example 271

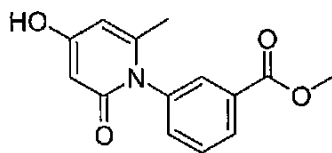
20



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoic acid.

5

Step 1: Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate .



10

Methyl 3-aminobenzoate (75.00 g, 496.13 mmol) and 4-hydroxy-6-methyl-2-pyrone (62.57 g, 496.13 mmol) were suspended in 1,2-dichlorobenzene (150 mL) and heated to 165 °C for 15 minutes. The reaction was cooled to room temperature and extracted with

15

0.54M K₂CO₃ (4 x 250 mL). The aqueous layers were acidified (pH 2) with 4N HCl. The precipitate was collected by filtration to afford a yellow-orange solid (20.24 g, 16%). The resulting filtrate was extracted with ethyl acetate (3 x 1 L). The organic layers were washed with brine (500 mL), dried

20

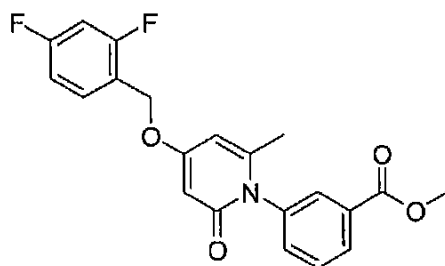
over MgSO₄ and evaporated. The resulting solid was washed with hot H₂O to afford a yellow-orange solid (3.84 g, 3%). The two solids were then combined. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.98

25

(dt, *J* = 1.31, 7.79 Hz, 1H), 7.69 (app t, *J* = 1.78 Hz, 1H), 7.62 (t, *J* = 7.78 Hz, 1H) 7.49 (ddd, *J* = 1.07, 1.07, 7.85 Hz, 1H), 5.89 (dd, *J* = 0.87, 2.48 Hz, 1H), 5.55 (app d, *J* = 0.94

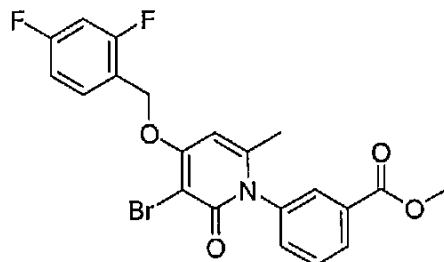
Hz, 1H), 3.83 (s, 3H), 1.80 (s, 3H). ES-HRMS m/z 260.0895 (M+H $C_{14}H_{13}NO_4$ requires 260.0917).

Step 2: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .



Methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (from step 1) (24.00 g, 92.57 mmol) and K_2CO_3 (15.35 g, 111.08 mmol) were dissolved in *N,N*-dimethylformamide (220 mL). 2,4-Difluorobenzyl bromide (20.12 g, 97.20 mmol) was then added and the reaction mixture stirred for 48 hours at room temperature. The reaction mixture was diluted with H_2O (1 L) and the precipitate collected by filtration to afford a white solid (4.08 g, 11%). The resulting oil was purified by chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford an off white solid (11.88 g, 33%). The two solids were combined. 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (dt, J = 1.41, 7.79 Hz, 1H), 7.87 (app t, J = 1.78 Hz, 1H), 7.58 (app t, J = 7.69 Hz, 1H) 7.45-7.38 (m, 2H), 6.94-6.84 (m, 2H), 5.97 (d, J = 2.68 Hz, 1H), 5.90 (ddd, J = 0.94, 1.74, 1.74 Hz, 1H), 5.97 (s, 1H), 3.90 (s, 3H), 1.89 (s, 3H). ES-HRMS m/z 386.1179 (M+H $C_{21}H_{17}F_2NO_4$ requires 386.1198).

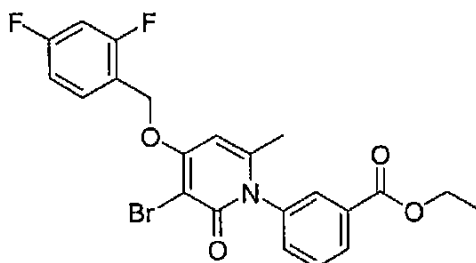
Step 3: Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 2) (15.85 g, 41.130 mmol)
 5 suspended in acetonitrile (165 mL) was cooled in an ice-bath. N-bromosuccinimide (7.687 g, 43.186 mmol) was added and the ice-bath was removed. The reaction mixture was stirred for 1.5 hours at room temperature. Reaction was concentrated and subjected to chromatography (silica gel, ethyl acetate with
 10 10% methanol/hexanes) afforded an off white solid (17.63 g, 92%). ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dt, *J* = 1.41, 7.85 Hz, 1H), 7.90 (t, *J* = 1.81 Hz, 1H), 7.67-7.41 (m, 3H), 7.05-6.88 (m, 2H), 6.13 (s, 1H), 5.30 (s, 2H), 3.95 (s, 1H), 2.01 (s, 3H). ES-HRMS *m/z* 464.0286 (M+H C₂₁H₁₆BrF₂NO₄ requires
 15 464.0304).

Step 4: Preparation of the title compound . Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 3) (10.0 g, 21.539 mmol) was dissolved
 20 in methanol (36 mL) and tetrahydrofuran (14 mL). 4N NaOH (13.5 mL, 53.847 mmol) was added. The resulting mixture was stirred for 1.5 hours at room temperature. The reaction was acidified (pH 2) with 4N HCl. The precipitate was collected by filtration to afford an off white solid (7.83 g, 81%) ¹H
 25 NMR (400 MHz, DMSO-*d*₆) δ 8.01 (dt, *J* = 1.41, 7.65 Hz, 1H), 7.76 (app t, *J* = 1.78 Hz, 1H), 7.76-7.15 (m, 5H), 6.66 (s, 1H), 5.32 (s, 2H), 1.92 (s, 3H). ES-HRMS *m/z* 450.0134 (M+H C₂₀H₁₄BrF₂NO₄ requires 450.0147).

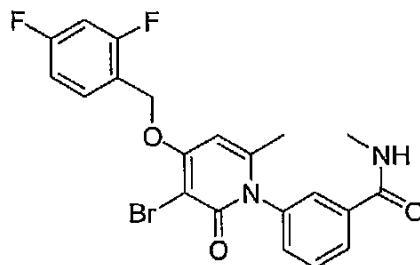
Example 272



5 Ethyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate

By following the method of Example 271 and substituting ethyl 3-aminobenzoate for methyl 3-aminobenzoate, the title compound was prepared (2.66 g, 79%). ¹H NMR (400 MHz, CDCl₃) δ 8.13 (dt, *J* = 1.41, 7.85 Hz, 1H), 7.84 (t, *J* = 1.88 Hz, 1H), 7.62-7.55 (m, 2H), 7.36 (app dq, *J* = 1.07, 7.85 Hz, 1H), 6.96 (app dt, *J* = 2.55, 8.35 Hz, 1H), 6.88-6.84 (m, 1H), 6.08 (s, 1H), 5.25 (s, 2H), 4.42-4.30 (m, 2H), 1.96 (s, 3H), 1.36 (t, *J* = 7.12 Hz, 3H). ES-HRMS *m/z* 478.0482 (M+H C₂₂H₁₈BrF₂NO₄ requires 15 478.0460).

Example 273

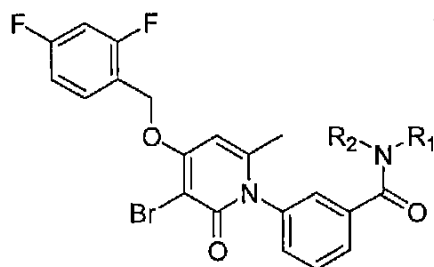


20 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-methylbenzamide

To a reaction vessel (borosilicate culture tube) was added EXAMPLE 271 (0.300 g, 0.666 mmol). A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylformamide (3 mL, 0.11 M) was added to the reaction vessel followed by approximately 5 0.97 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional *N,N*-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. *N*-10 Methylamine in tetrahydrofuran (0.50 mL, 0.999 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (30 mL) and treated with approximately 2.0 g of polyamine resin (2.63 15 mmol/g) and approximately 3.6 g of methylisocyanate functionalized polystyrene (1.10 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched 20 byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N₂ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give an off-white solid 25 (0.189 g, 61%). ¹H NMR (400 MHz, DMF-*d*₆) δ 8.56 (br d, *J* = 4.16 Hz, 1H), 8.05-7.76 (m, 3H), 7.66 (t, *J* = 7.79 Hz, 1H), 7.56-7.19 (m, 3H), 6.74 (s, 1H), 5.43 (s, 2H), 3.46 (s, 3H), 2.03 (s, 3H). ES-HRMS *m/z* 463.0476 (M+H C₂₁H₁₇BrF₂N₂O₃ requires 463.0463).

30

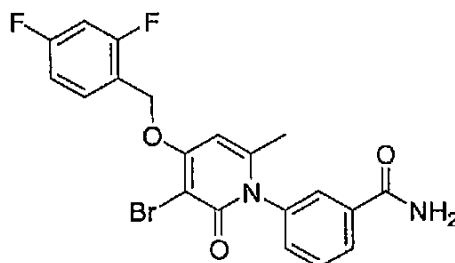
Preparation of Example 274-289



By following the method of Example 273 and replacing N-methylamine with the appropriate amine, the compounds of
 5 Examples 274-289 are prepared. The deprotection of the protected intermediates was accomplished with 4N HCl in dioxane to afford the compounds as their hydrochloride salts.

Compound No.	R1	R2	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 274	CH ₂ CH ₂ NH-	CH ₂ CH ₂ NH-	92.8	C ₂₄ H ₂₂ BrF ₂ N ₃ O ₃	518.0885	518.0865
Ex. 275	H	CH ₂ CH ₂ NH ₂	95.7	C ₂₂ H ₂₀ BrF ₂ N ₃ O ₃	492.0729	492.0711
Ex. 276	H	CH ₂ CH ₂ CH ₂ NH ₂	97.8	C ₂₃ H ₂₂ BrF ₂ N ₃ O ₃	506.0885	506.0889
Ex. 277	H	OH	91.0	C ₂₀ H ₁₅ BrF ₂ N ₂ O ₄	465.0256	465.0278
Ex. 278	CH ₃	CH ₃	67.7	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₃	477.0620	477.0626
Ex. 279	CH ₂ CH ₂ O-	CH ₂ CH ₂ O-	86.7	C ₂₄ H ₂₁ BrF ₂ N ₂ O ₄	519.0726	519.0696
Ex. 280	H	CH ₂ CH ₂ OH	78.3	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₄	493.0569	493.0575
Ex. 281	CH ₂ CH ₂ CH ₂ -	CH ₂ CH ₂ CH ₂ -	87.9	C ₂₅ H ₂₃ BrF ₂ N ₂ O ₃	517.0933	517.0918
Ex. 282	H	CH(CH ₃) ₂	80.6	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₃	491.0776	491.0797
Ex. 283	CH ₂ CH ₂ -	CH ₂ CH ₂ -	87.9	C ₂₄ H ₂₁ BrF ₂ N ₂ O ₄	503.0776	503.0732
Ex. 284	CH ₂ CH ₂ N(CH ₃)-	CH ₂ CH ₂ N(CH ₃)-	75.8	C ₂₅ H ₂₄ BrF ₂ N ₃ O ₃	532.1042	532.1038
Ex. 285	H	CH ₂ CH ₂ N(CH ₃) ₂	86.1	C ₂₄ H ₂₄ BrF ₂ N ₃ O ₃	520.1042	520.1030
Ex. 286	H	CH ₂ CH ₂ OCH ₃	90.2	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₄	507.0726	507.0680
Ex. 287	CH ₃	CH ₂ CH ₂ N(CH ₃) ₂	60.0	C ₂₅ H ₂₆ BrF ₂ N ₃ O ₃	534.1198	534.1155
Ex. 288	CH ₃	CH ₂ CH ₂ OH	81.6	C ₂₃ H ₂₁ BrF ₂ N ₂ O ₄	507.0726	507.0694
Ex. 289	CH ₃	CH ₂ CH ₂ OCH ₃	94.4	C ₂₄ H ₂₃ BrF ₂ N ₂ O ₄	521.0882	521.0862

Example 290

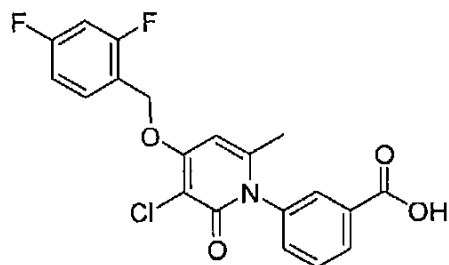


5

3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzamide

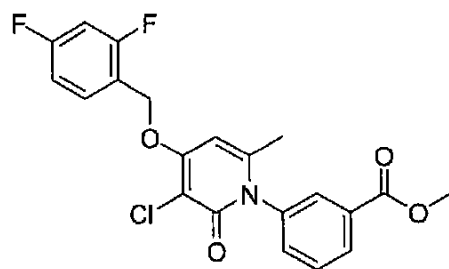
10 EXAMPLE 271 (2.00 g, 4.44 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (0.94 g, 5.33 mmol) were suspended in tetrahydrofuran (20 mL). 4-Methylmorpholine (1.5 mL, 13.32 mmol) was added. The resulting mixture was stirred for 1.5 hours at room temperature. NH_4OH (10 mL, 148.00 mmol) was
 15 added and the reaction was stirred for 0.5 hours at room temperature. H_2O (50 mL) and tetrahydrofuran (50 mL) were added and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (75 mL) and the combined organics were washed with saturated Na_2CO_3 (50 mL), 1N HCl (50
 20 mL), and brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated. The resulting solid was washed with diethyl ether to give a white solid (1.86 g, 93%). ^1H NMR (400 MHz, $\text{DMF}-d_6$) δ 8.20 (br s, 1H), 8.10-8.07 (m, 1H), 7.79 (s, 1H), 7.79 (app q, $J = 7.83$ Hz, 1H), 7.66 (app t, $J = 7.79$ Hz, 1H), 7.57-7.54 (m, 1H), 7.46 (br s, 1H), 7.36-7.19 (m, 2H), 6.74 (s, 1H), 5.43 (s, 2H), 2.04 (s, 3H). ES-HRMS m/z 449.0307 ($\text{M}+\text{H}$ $\text{C}_{20}\text{H}_{15}\text{BrF}_2\text{N}_2\text{O}_3$ requires 449.0307).

Example 291



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-
 5 1(2H)-yl]benzoic acid

Step 1: Preparation of methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate



10

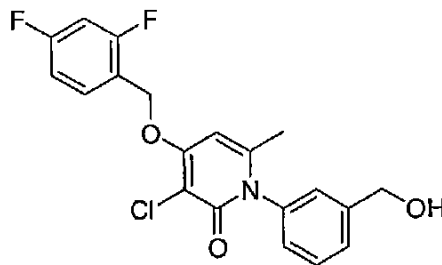
The product from step 2, Example 271 (4.54 g, 11.78 mmol) and *N*-chlorosuccinimide (1.65 g, 12.37 mmol) were suspended in dichloromethane (12 mL). Dichloroacetic acid (0.10 mL, 1.22
 15 mmol) was added and the reaction mixture was stirred overnight at 40 °C. The reaction was cooled to room temperature and a precipitate formed. The precipitate was collected by filtration and washed with dichloromethane (3 x 10 mL) to afford a white solid (1.75 g, 35%). The filtrate was
 20 concentrated and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afforded an off white solid (1.29 g, 26%). The two solids were then combined.
¹H NMR (400 MHz, CDCl₃) δ 8.12 (dt, *J* = 1.38, 7.83 Hz, 1H), 7.85 (t, *J* = 1.74 Hz, 1H), 7.60-7.52 (m, 2H), 7.37 (dq, *J* =

0.92, 7.92 Hz, 2H), 6.95 (app dt, $J = 2.55$, 8.32 Hz, 1H), 6.89-6.83 (m, 1H), 6.11 (s, 1H), 5.24 (s, 2H), 3.90 (s, 3H), 1.96 (s, 3H). ES-HRMS m/z 420.0783 ($M+H$ $C_{21}H_{16}ClF_2NO_4$ requires 420.0809).

5

Step 2: Methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 1) (2.90 g, 6.91 mmol) was dissolved in methanol (5 mL) and tetrahydrofuran (12 mL). 4N NaOH (4.3 mL, 17.27 mmol) was added. The resulting mixture was stirred for 1.5 hours at room temperature. The reaction was acidified (pH=2) with 4N HCl. The precipitate was collected by filtration to afford an off white solid (2.36 g, 84%). 1H NMR (400 MHz, DMSO- d_6) δ 8.01 (dt, $J = 1.41$, 7.65 Hz, 1H), 7.76 (app t, $J = 1.68$ Hz, 1H), 7.69-7.53 (m, 3H), 7.36-7.14 (m, 2H), 6.69 (s, 1H), 5.32 (s, 2H), 1.93 (s, 3H). ES-HRMS m/z 406.0662 ($M+H$ $C_{20}H_{14}ClF_2NO_4$ requires 406.0652).

20 Example 292



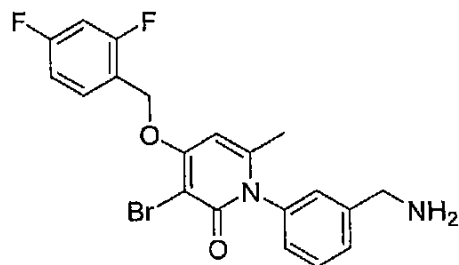
3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

25

The starting material (0.550 g, 1.540 mmol) and *N*-chlorosuccinimide (0.214 g, 1.602 mmol) were suspended in dichloromethane (15 mL). Dichloroacetic acid (0.01 mL, 0.154

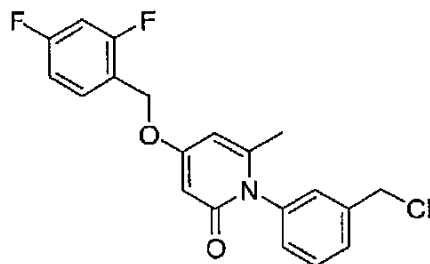
mmol) was added and the reaction mixture heated to 40 °C for 9 hours. The reaction was cooled to room temperature and a precipitate formed. The precipitate was collected by filtration and washed with dichloromethane (3 x 10 mL) to afford a white solid (0.286 g, 47%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.38 (*app* q, *J* = 7.35 Hz, 1H), 7.30-7.24 (m, 2H), 7.00 (br s, 1H), 6.85 (*app* dt, *J* = 2.37, 6.24 Hz, 1H), 6.82-6.67 (m, 2H), 6.01 (s, 1H), 5.07 (s, 2H), 4.48 (d, *J* = 5.24 Hz, 2H), 1.81 (*app* d, *J* = 0.40 Hz, 3H). ES-HRMS *m/z* 392.0885 (M+H C₂₀H₁₆ClF₂NO₃ requires 392.0860).

Example 293



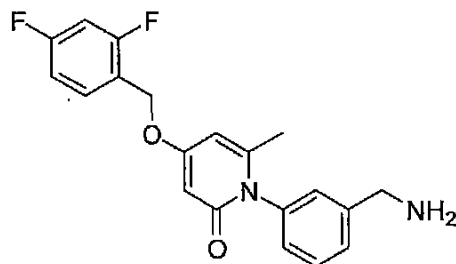
1-[3-(aminomethyl)phenyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.



2,4,6-Trichloro-[1,3,5]-triazine (3.09 g, 16.78 mmol) was dissolved in *N,N*-dimethylformamide (45 mL). The reaction mixture was stirred at room temperature for 1 hour and then dichloromethane (90 mL) was added. The alcohol (5.72 g, 15.99 mmol) was then added. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with dichloromethane (200 mL) and the organic phase was washed with H₂O (200 mL), saturated Na₂CO₃ (200 mL), 1N HCl (200 mL), and brine (200 mL). The organic phase was dried over MgSO₄ and evaporated to give an orange solid (5.95 g, 99%).

Step 2: Preparation of 1-[3-(aminomethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one.



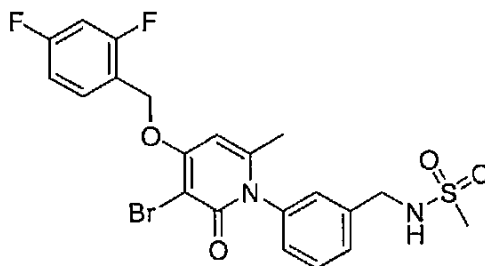
1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one from step 1 (1.00 g, 2.66 mmol) was suspended in methanol (5 mL). The suspension was then brought to -78 °C and NH₃ was bubbled through the reaction mixture for 10 minutes. The reaction was then slowly allowed to warm to room temperature and stirred at room temperature for 4 days. The reaction was concentrated and the residue taken up in CH₂Cl₂ and filtered to remove excess salt. The filtrate was concentrated to afford a tan solid (0.94 g, 99%).

Step 3: Preparation of title compound . 1-[3-(aminomethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-

methypyridin-2(1H)-one from step 3 (3.89 g, 10.93 mmol) suspended in acetonitrile (42 mL) was cooled in an ice-bath. *N*-bromosuccinimide (2.04 g, 11.47 mmol) was added and the ice-bath was removed. The reaction mixture was stirred for 1.5
5 hours at room temperature. The reaction was diluted with acetonitrile (100 mL) and the precipitate that formed was collected by filtration and washed with acetonitrile (3 x 30 mL) to afford an off-white solid (2.74 g, 58%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67-7.59 (m, 3H), 7.34-7.31 (m, 2H), 7.04 (app
10 t, *J* = 8.72 Hz, 2H), 7.05-6.88 (m, 2H), 6.13 (s, 1H), 5.30 (s, 2H), 3.95 (s, 1H), 2.01 (s, 3H). ES-HRMS *m/z* 435.0538 (M+H C₂₀H₁₇BrF₂N₂O₂ requires 435.0514).

Example 294

15

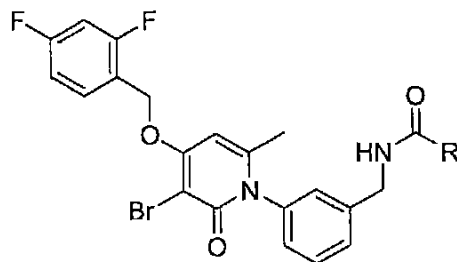


N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-
20 oxopyridin-1(2H)-yl]benzyl}methanesulfonamide

To a reaction vessel (borosilicate culture tube) was added
EXAMPLE 293 (0.200 g, 0.459 mmol) and *N,N*-dimethylformamide (4
mL). A stock solution of 4-methylmorpholine in *N,N*-
25 dimethylformamide (1.8 mL, 1.0 M) was added to the reaction
vessel and the parallel reaction apparatus was then orbitally
shaken (Labline Benchtop Orbital Shaker) at approximately 200
RPM at room temperature for 10 minutes. A stock solution of

methanesulfonyl chloride in *N,N*-dimethylformamide (4.50 mL, 0.15 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature for 2 hours. At this time the reaction was diluted with
5 dichloromethane (4 mL) and treated with approximately 2.1 g of polyamine resin (2.63 mmol/g) and approximately 0.8 g of methylisocyanate functionalized polystyrene (1.7 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature overnight. The reaction vessel was then opened
10 and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with dichloromethane (2 x 5 mL). The filtrate was evaporated by blowing N₂ over the vial while
15 heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) to give a yellow solid (0.190 g, 81%). ¹H NMR (400 MHz, CD₃OD) δ 7.63 (*app* q, *J* = 7.00 Hz, 1H), 7.56-7.50 (m, 2H), 7.25 (m, 1H), 7.16 (dt, *J* = 1.94, 7.25 Hz, 1H), 7.04 (*app* t, *J* = 8.59 Hz, 2H), 6.58 (s, 1H), 5.34 (s, 2H), 4.30 (s, 2H), 2.87 (s,
20 3H), 2.03 (s, 3H). ES-HRMS *m/z* 513.0313 (M+H C₂₁H₁₉BrF₂N₂O₄S requires 513.0290).

Preparation of Example 295-296

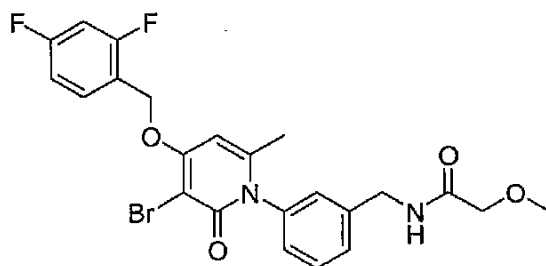


By following the method of Example 294 and replacing methanesulfonyl chloride with the appropriate acid chloride, the compounds of Examples 295-296 are prepared.

Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 295	CH ₃	78.0	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₃	477.0620	477.0640
Ex. 296	OCH ₃	84.0	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₄	493.0569	493.0591

5

Example 297



10

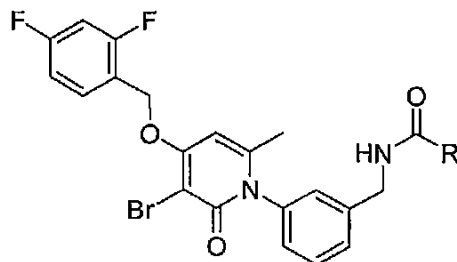
N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-2-methoxyacetamide

15 To a reaction vessel (borosilicate culture tube) was added approximately 2.87 g of polymer bound carbodiimide resin (0.96 mmol/g) followed by a stock solution of methoxyacetic acid (8.0 mL, 0.10 M) in *N,N*-dimethylacetamide. A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylacetamide (3.0 mL, 0.10 M) and *N*-methylmorpholine (6.0 mL, 0.10 M) in 1,2-dichloroethane were added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 4 hours. A stock solution of EXAMPLE 293 in

20

N,N-dimethylacetamide (5.0 mL, 0.10 M) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with 1,2-dichloroethane (10 mL) and
5 treated with approximately 1.70 g of polyamine resin (2.63 mmol/g) and approximately 0.84 g of methylisocyanate functionalized polystyrene (1.50 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution
10 phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After partial evaporation the insoluble byproducts were rinsed with *N,N*-dimethylacetamide (2 x 5 mL). The filtrate was evaporated by blowing N₂ over the vial while heating (60 °C) in a reaction
15 block (KEM-Lab Parallel Reactor) and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off white solid (0.081 g, 28%).
¹H NMR (400 MHz, DMF-*d*₆) δ 7.59 (q, *J* = 7.65 Hz, 1H), 7.46 (app t, *J* = 7.55 Hz, 1H), 7.40-7.37 (m, 1H), 7.11-7.07 (m, 2H),
20 7.00 (t, *J* = 8.56 Hz, 2H), 6.54 (s, 1H), 5.30 (s, 2H), 4.43 (s, 2H), 3.88 (s, 2H), 3.35 (app d, *J* = 0.80 Hz, 2H), 1.97 (s, 3H). ES-HRMS *m/z* 507.0699 (M+H C₂₃H₂₁BrF₂N₂O₄ requires 507.0726).

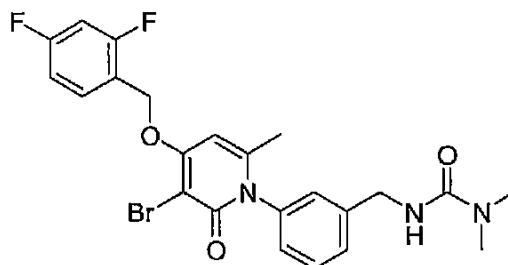
25 Preparation of Examples 298-300



By following the method of and replacing methoxyacetic acid with the appropriate acid, the compounds of Examples 298-300 are prepared. The deprotection of the protected intermediates was accomplished with 4N HCl in dioxane or 1 M K₂CO₃ in methanol to afford the compounds as hydrochloride salts.

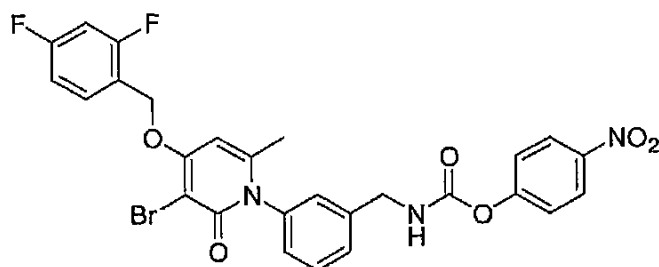
Compound No.	R	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 298	CH ₂ OCOCH ₃	35.5	C ₂₄ H ₂₁ BrF ₂ N ₂ O ₅	535.0675	535.0686
Ex. 299	CH ₂ NH ₂	32.6	C ₂₂ H ₂₀ BrF ₂ N ₃ O ₃	492.0729	492.0744
Ex. 300	CH ₂ OH	33.4	C ₂₂ H ₁₉ BrF ₂ N ₂ O ₄	493.0569	493.0578

Example 301



N'-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzyl}-N,N-dimethylurea

Step 1: Preparation of 4-nitrophenyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzylcarbamate.



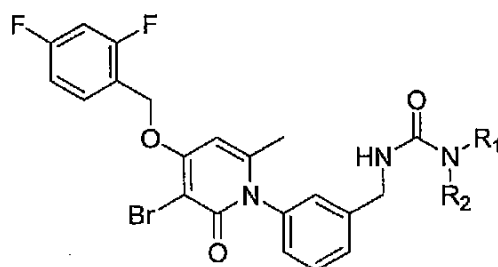
1 - [3 - (aminomethyl)phenyl] - 3 - bromo - 4 - [(2,4 - difluorobenzyl)oxy] -
 6 - methylpyridin - 2 (1H) - one (1.08 g, 2.48 mmol) was suspended in
 5 dichloromethane (7.5 mL). Pyridine was added (0.222 mL, 2.74
 mmol). After stirring for 10 minutes at room temperature, a
 stock solution of 4 - nitrophenyl chloroformate (5.0 mL, 0.50 M)
 in dichloromethane was added dropwise. After stirring for 4.5
 hours at room temperature, a stock solution of 4 - nitrophenyl
 10 chloroformate (2.5 mL, 0.50 M) in dichloromethane was again
 added dropwise and stirring continued at room temperature
 overnight. The reaction mixture was concentrated and
 subjected to chromatography (silica gel, ethyl acetate with
 10% methanol/hexanes) afforded a yellow solid (0.85 g, 57%).

15

Step 2: Preparation of title compound . To a reaction vessel
 (borosilicate culture tube) was added 4 - nitrophenyl 3 - [3 -
 bromo - 4 - [(2,4 - difluorobenzyl)oxy] - 6 - methyl - 2 - oxopyridin - 1 (2H) -
 yl]benzylcarbamate (from step 1) (0.150 g, 0.250 mmol) and
 20 dichloromethane (2.5 mL). The parallel reaction apparatus was
 then orbitally shaken (Labline Benchtop Orbital Shaker) at
 approximately 200 RPM at room temperature for 15 minutes. A
 stock solution of *N,N* - dimethylamine in tetrahydrofuran (0.15
 mL, 2.0 M) was then added to the reaction vessel and the
 25 reaction apparatus was orbitally shaken at room temperature
 overnight. The reaction mixture was concentrated and
 subjected to chromatography (silica gel, ethyl acetate with
 10% methanol/hexanes) which afforded an off white solid (0.065

g, 51%). ^1H NMR (400 MHz, DMF-d_6) δ 7.58 (*app* q, $J = 7.79$ Hz, 1H), 7.42 (*app* t, $J = 7.65$ Hz, 1H), 7.37 (*app* d, $J = 7.79$ Hz, 1H), 7.08 (s, 1H), 7.03 (*app* dt, $J = 1.58, 5.37$ Hz, 1H), 6.96 (*app* dt, $J = 2.55, 8.39$ Hz, 1H), 6.88-6.83 (m, 1H), 6.06 (s, 1H), 5.24 (s, 2H), 4.95 (*app* t, $J = 5.57$ Hz, 1H), 4.42 (*app* dddd, $J = 5.10, 5.71, 10.20, 15.17$ Hz, 2H), 2.90 (s, 6H), 1.96 (s, 3H). ES-HRMS m/z 506.0848 ($\text{M}+\text{H}$ $\text{C}_{23}\text{H}_{22}\text{BrF}_2\text{N}_3\text{O}_3$ requires 506.0885).

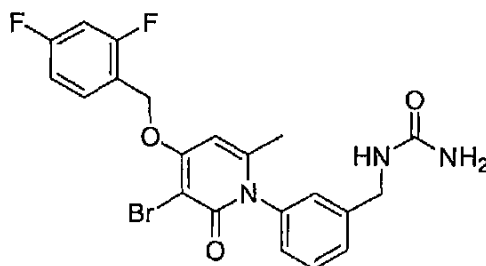
10 Preparation of Examples 302-303



By following the method of Example 301 and substituting *N,N*-dimethylamine with the appropriate amine, the compounds of Examples 302-303 are prepared.

Compound No.	R ₁	R ₂	% Yield	MF	M+H Requires	ES-HRMS m/z
Ex. 302	H	CH ₃	52.3	$\text{C}_{22}\text{H}_{20}\text{BrF}_2\text{N}_3\text{O}_3$	492.0729	492.0737
Ex. 303	CH ₂ CH ₂ O-	CH ₂ CH ₂ O-	50.7	$\text{C}_{25}\text{H}_{24}\text{BrF}_2\text{N}_3\text{O}_4$	548.0991	548.0962

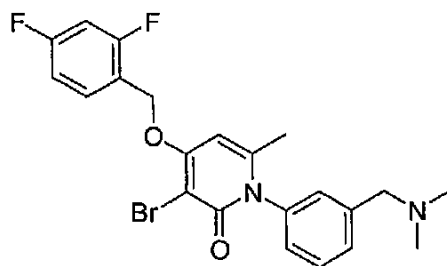
Example 304



N-{3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-
 5 oxopyridin-1(2H)-yl]benzyl}urea

To a reaction vessel (borosilicate culture tube) was added
 EXAMPLE 293 (0.200 g, 0.459 mmol) and tetrahydrofuran (4.0
 mL). A stock solution of 4-methylmorpholine in
 10 tetrahydrofuran (1.8 mL, 1.0 M) was added to the reaction
 vessel and the parallel reaction apparatus was then orbitally
 shaken (Labline Benchtop Orbital Shaker) at approximately 200
 RPM at room temperature for 10 minutes. A stock solution of
 trimethylsilyl isocyanate in tetrahydrofuran (4.0 mL, 0.2 M)
 15 was then added to the reaction vessel and the reaction
 apparatus was orbitally shaken at room temperature for two
 hours. At this time the reaction was diluted with
 tetrahydrofuran (4.0 mL) and the resulting precipitate
 collected by filtration. The solid was then washed with
 20 tetrahydrofuran (3 x 5 mL) to afford a white solid (0.214 g,
 97%). ¹H NMR (400 MHz, CD₃OD) δ 7.72 (app q, J = 7.83 Hz, 1H),
 7.55 (app t, J = 8.06 Hz, 1H), 7.46 (d, J = 7.52 Hz, 1H),
 7.25-7.14 (m, 4H), 6.65 (s, 1H), 5.65 (app t, J = 0.80 Hz,
 1H), 5.40 (s, 2H), 4.38 (s, 2H), 2.05 (s, 3H). ES-HRMS m/z
 25 478.0594 (M+H C₂₁H₁₈BrF₂N₃O₃ requires 478.0572).

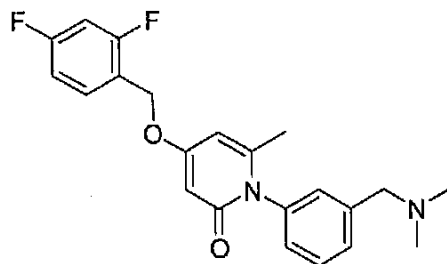
Example 305



5 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-
[(dimethylamino)methyl]phenyl]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-[3-
[(dimethylamino)methyl]phenyl

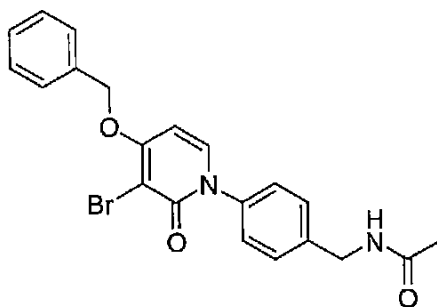
10 }-6-methylpyridin-2(1H)-one.



15 1-[3-(chloromethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-
methylpyridin-2(1H)-one (from step 1 of the synthesis of
EXAMPLE 293) (0.500 g, 1.330 mmol) was suspended in a stock
solution of *N,N*-dimethylamine in methanol (2.0 mL, 2.0 M) and
stirred overnight at room temperature. Reaction was
concentrated and the residue partitioned between H₂O (25 mL)
20 and ethyl acetate (25 mL). The aqueous layer was further
extracted with ethyl acetate (2 x 30 mL), and the combined
organics were washed with brine (30 mL), dried over MgSO₄, and
concentrated to afford an off-white solid (0.508 g, 99%).

Step 2: Preparation of the title compound . 4-[(2,4-difluorobenzyl)oxy]-1-{3-[(dimethylamino)methyl]phenyl}-6-methylpyridin-2(1H)-one from step 1 (0.200 g, 0.521 mmol) was suspended in acetonitrile (2.5 mL) and cooled in an ice-bath. 5 N-bromosuccinimide (0.097 g, 0.547 mmol) was added and the ice-bath was removed. The reaction mixture was stirred for 1.5 hours at room temperature. The reaction was diluted with acetonitrile (100 mL). The precipitate that formed was collected by filtration and washed with acetonitrile (3 x 15 10 mL) to afford a yellow solid (0.160 g, 66%). Chromatography (C-18, acetonitrile/H₂O with 0.1% trifluoroacetic acid, followed by chromatography silica gel, ethyl acetate with 10% methanol/hexanes) afforded an off-white solid (0.024 g, 10%).
¹H NMR (400 MHz, CD₃OD) δ 7.68 (app q, J = 7.85 Hz, 1H), 7.58 (app t, J = 7.65 Hz, 1H), 7.50 (app d, J = 7.85 Hz, 1H), 7.25-7.05 (m, 4H), 6.63 (s, 1H), 5.39 (s, 2H), 3.61 (app q, J = 12.08 Hz, 2H), 2.32 (s, 6H), 2.08 (s, 3H). ES-HRMS m/z 463.0782 (M+H C₂₂H₂₁BrF₂N₂O₂ requires 463.0827).

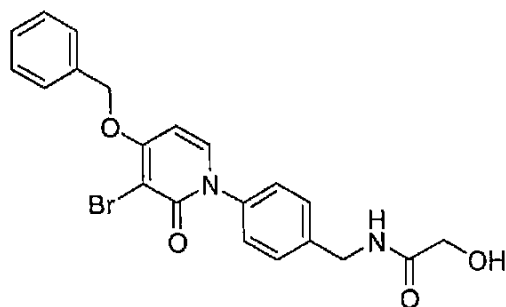
20 Example 306



25 N-{4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzyl}acetamide

1- [4- (aminomethyl)phenyl] -4- (benzyloxy) -3-bromopyridin-2 (1H) -
one hydrochloride (0.150 g, 0.389 mmol) was dissolved in *N,N*-
dimethylformamide (3.5 mL). A stock solution of 4-
methylmorpholine in *N,N*-dimethylformamide (1.5 mL, 1.0 M) was
5 added and the reaction stirred at room temperature for 10
minutes. A stock solution of acetyl chloride in *N,N*-
dimethylformamide (3.0 mL, 0.2 M) was then added to the
reaction vessel and the reaction apparatus was orbitally
shaken at 200 RPM for 2 hours at room temperature. At this
10 time the reaction was diluted with dichloromethane (4 mL) and
treated with approximately 1.8 g of polyamine resin (2.63
mmol/g) and approximately 0.8 g of methylisocyanate
functionalized polystyrene (1.7 mmol/g) and the orbital
shaking was continued at 200 RPM at room temperature
15 overnight. The reaction vessel was then opened and the
solution phase products were separated from the insoluble
quenched byproducts by filtration and collection into a vial.
After partial evaporation the insoluble byproducts were
further rinsed with dichloromethane (3 x 5 mL) and combined
20 with the partially concentrated filtrate. The resulting
filtrate was concentrated by blowing N₂ over the vial while
heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor)
to give an off-white solid (0.083 g, 50%). ¹H NMR (400 MHz,
CD₃OD) δ 7.59 (d, *J* = 7.79 Hz, 1H), 7.48-7.29 (m, 9H), 6.55 (d,
25 *J* = 7.79 Hz, 1H), 5.35 (s, 2H), 4.39 (s, 2H), 1.98 (s, 3H).
ES-HRMS *m/z* 427.0625 (M+H C₂₁H₁₉BrN₂O₃ requires 427.0652).

Example 307

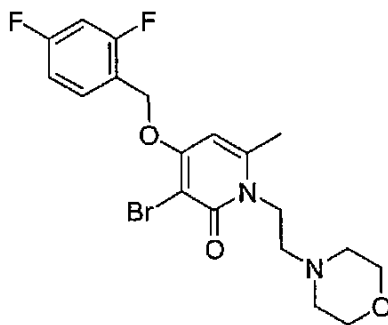


N-{4-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]benzyl}-2-
 5 hydroxyacetamide

To a reaction vessel (borosilicate culture tube) was added approximately 1.95 g of polymer bound carbodiimide resin (0.96 mmol/g) followed by a stock solution of glycolic acid
 10 (5.8 mL, 0.10 M) in *N,N*-dimethylacetamide. A stock solution of 1-hydroxybenzotriazole in *N,N*-dimethylacetamide (0.4 mL, 0.10 M) and *N*-methylmorpholine in 1,2-dichloroethane (3.9 mL, 0.10 M) were added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop
 15 Orbital Shaker) at approximately 200 RPM at room temperature for 2 hours. A stock solution of 1-[4-(aminomethyl)phenyl]-4-(benzyloxy)-3-bromopyridin-2(1H)-one hydrochloride in *N,N*-dimethylacetamide (0.05 M, 7.8 mL) was then added to the reaction vessel and the reaction apparatus was orbitally
 20 shaken at room temperature overnight. At this time the reaction was diluted with 1,2-dichloroethane (8 mL) and treated with approximately 1.17 g of polyamine resin (2.63 mmol/g) and approximately 0.58 g of methylisocyanate functionalized polystyrene (1.50 mmol/g) and the orbital
 25 shaking was continued at 200 RPM at room temperature for 4 hours. The reaction vessel was then opened and the solution phase products were separated from the insoluble quenched byproducts by filtration and collection into a vial. After

partial evaporation the insoluble byproducts were rinsed with *N,N*-dimethylacetamide (2 x 5 mL) and combined with the partially concentrated filtrate. The filtrate was concentrated by blowing N₂ over the vial while heating (60 °C) in a reaction block (KEM-Lab Parallel Reactor) and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) which afforded an off white solid (0.081 g, 21%). ¹H NMR (400 MHz, CD₃OD) δ 7.55-7.30 (m, 10H), 6.51 (d, *J* = 7.85 Hz, 1H), 5.37 (s, 2H), 4.52 (s, 2H), 4.08 (s, 2H). ES-
10 HRMS *m/z* 443.0605 (M+H C₂₁H₁₉BrN₂O₄ requires 443.0601).

Example 308



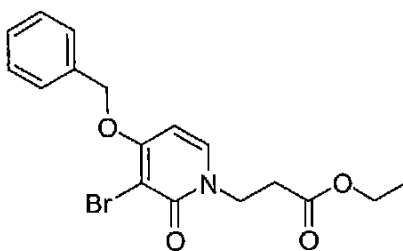
15

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-morpholin-4-ylethyl)pyridin-2(1H)-one

20 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.100 g, 0.303 mmol), cesium carbonate (0.296 g, 0.909 mmol), and 4-(2-chloroethyl)morpholine (0.059 g, 0.394 mmol) were suspended in acetonitrile (4 mL). The reaction was stirred at 60 °C overnight. H₂O (25 mL) was added and the resulting
25 precipitate was collected by filtration. The solid was subjected to chromatography (silica gel, ethyl acetate with 10% methanol) afforded an off-white solid (0.040 g, 30%). ¹H

NMR (400 MHz, CDCl₃) δ 7.55 (app q, J = 7.92 Hz, 1H), 6.93 (app t, J = 8.39 Hz, 1H), 6.84 (app t, J = 9.40 Hz, 1H), 5.95 (s, 1H), 5.18 (s, 2H), 4.16 (app t, J = 6.78 Hz, 2H), 3.68 (s, 4H), 2.65 (app t, J = 6.38 Hz, 2H), 2.54 (s, 4H), 2.43 (s, 3H). ES-HRMS m/z 443.0743 (M+H C₁₉H₂₁BrF₂N₂O₃ requires 443.0776).

Example 309



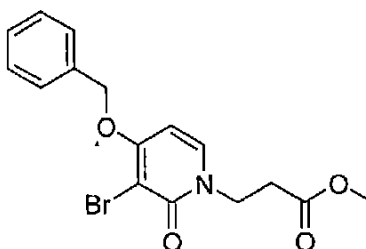
ethyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-yl]propanoate

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.50 g, 1.78 mmol) and cesium fluoride (0.0027 g, 0.178 mmol) were suspended in tetrahydrofuran (10 mL) followed by dropwise addition of tetraethylortho silicate (0.37 g, 1.78 mmol) at room temperature. After stirring for 10 minutes at room temperature, ethyl acrylate (0.23 g, 2.32 mmol) was added dropwise and the reaction stirred at room temperature overnight. The reaction mixture was filtered through a pad of Celite®. The filtrate was concentrated and the resulting residue subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexanes) to afford a white solid (0.62 g, 92%). ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, J = 7.79 Hz, 1H), 7.41-7.29 (m, 5H), 6.03 (d, J = 7.65 Hz, 1H), 5.20 (s, 2H), 4.17 (t, J = 5.98 Hz, 2H), 4.07 (q, J = 7.16 Hz, 2H), 2.83 (t,

$J = 5.98$ Hz, 2H), 1.19 (t, $J = 7.18$ Hz, 3H). ES-HRMS m/z 380.0523 ($M+H$ $C_{17}H_{18}BrNO_4$ requires 380.0492).

Example 310

5

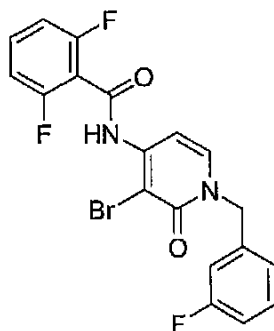


methyl 3-[4-(benzyloxy)-3-bromo-2-oxopyridin-1(2H)-
yl]propanoate

10

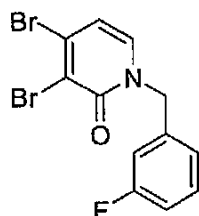
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-
2(1H)-one (5.00 g, 17.85 mmol) and cesium fluoride (0.27 g,
1.78 mmol) were suspended in tetrahydrofuran (50 mL) followed
by dropwise addition of tetramethyloxy silicate (2.70 g,
15 17.85 mmol) at room temperature. After stirring for 10
minutes at room temperature, methyl acrylate (2.00 g, 23.20
mmol) was added dropwise and the reaction stirred at room
temperature for 48 hours. The reaction mixture was filtered
through a pad of Celite®. The filtrate was concentrated and
20 the resulting residue subjected to chromatography (silica gel,
ethyl acetate with 10% methanol/hexanes) to afford a white
solid (6.10 g, 93%). 1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, $J =$
7.65 Hz, 1H), 7.41-7.29 (m, 5H), 6.04 (d, $J = 7.65$ Hz, 1H),
5.20 (s, 2H), 4.17 (t, $J = 5.91$ Hz, 2H), 3.63 (s, 3H), 2.85
25 (t, $J = 5.91$ Hz, 2H). ES-HRMS m/z 366.0350 ($M+H$ $C_{16}H_{16}BrNO_4$
requires 366.0335).

Example 311



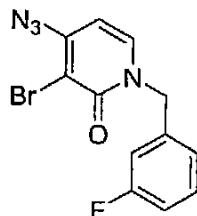
5
N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-
2,6-difluorobenzamide

Step 1: Preparation of 3,4-dibromo-1-(3-fluorobenzyl)pyridin-
10 2(1H)-one.



3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl
15 trifluoromethanesulfonate (2.00 g, 4.65 mmol), KBr (5.53 g,
46.49 mmol), and 18-Crown-6 (0.10 g, 0.38 mmol) were dissolved
in *N,N*-dimethylacetamide (26 mL). The reaction mixture was
then heated at reflux for 16 hours. The reaction was
concentrated and the resulting residue was partition between
20 water (50 mL) and ethyl acetate (3 X 50 mL). The combined
organics were washed with H₂O (2 X 30 mL), brine (50 mL), dried
over MgSO₄, concentrated, and subjected to chromatography
(silica gel, ethyl acetate with 10% methanol/hexane) to afford
a brown solid (0.850 g, 51%).

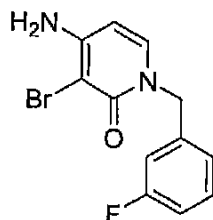
Step 2: Preparation of 4-azido-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one.



5

Sodium azide (1.08 g, 16.62 mmol) was suspended in *N,N*-dimethylformamide (10 mL) and a stock solution of 3,4-dibromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 1) in *N,N*-dimethylformamide (33.0 mL, 0.33 M) was added and the resulting mixture was heated to 60 °C for 4 hours. Ice water (30 mL) was added and the aqueous layer was extracted with ethyl acetate (4 X 50 mL). The combined organics were washed with H₂O (3 X 50 mL), brine (2 X 25 mL), dried over MgSO₄, concentrated, and subjected to chromatography (silica gel, ethyl acetate with 10% methanol/hexane) to afford an off-white solid (3.50 g, 98%).

Step 3: Preparation of 4-amino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one hydrochloride



4-azido-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 2) (4.00 g, 12.38 mmol) was suspended in ethyl acetate (300 mL) and Fe (2.07 g, 37.14 mmol) was added. A stock solution

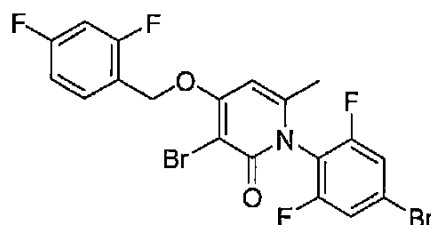
of NH_4Cl in H_2O (300 mL, 0.2 M) was added and the reaction mixture was stirred at room temperature for 36 hours. The reaction was filtered through a pad of Celite® and concentrated. The resulting solid was dissolved in ethyl acetate (150 mL) and washed with water (3 X 50 mL), brine (50 mL), dried over MgSO_4 , and concentrated. ^1H NMR (400 MHz, CD_3OD) δ 7.38-7.29 (m, 2H), 7.05 (d, $J = 7.79$ Hz, 1H), 6.99 (d, $J = 8.99$ Hz, 2H), 6.03 (d, $J = 7.39$ Hz 1H), 5.09 (s, 2H). ES-HRMS m/z 297.0023 ($\text{M}+\text{H}$ $\text{C}_{20}\text{H}_{17}\text{BrF}_2\text{N}_2\text{O}_2$ requires 297.0033).

10

Step 4: Preparation of the title compound . 4-amino-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one (from step 3) (0.30 g, 1.01 mmol) and 4-dimethylaminopyridine (0.002 g, 0.01 mmol) were suspended in acetonitrile (5 mL) followed by dropwise addition of triethylamine (0.2 mL, 1.41 mmol). This reaction mixture was stirred for 10 minutes at room temperature before being cooled to 0 °C. 2,6-difluorobenzoyl chloride (0.37 g, 2.12 mmol) was added dropwise and the reaction was heated at reflux overnight. The reaction was cooled to room temperature and 1N NaOH (10 mL) was added. The reaction was then stirred for 45 minutes at room temperature. The reaction mixture was extracted with ethyl acetate (3 x 25 mL) and the organic layer washed with 1N NaOH (2 X 25 mL), H_2O (until pH neutral), brine (50 mL), dried over MgSO_4 , concentrated, and subjected to chromatography (on C-18, acetonitrile/ H_2O with 0.1% trifluoroacetic acid) to afford a white solid (0.19 g, 43%). ^1H NMR (400 MHz, CDCl_3) δ 8.42 (br s, 1H), 7.67 (d, $J = 7.65$ Hz, 1H), 7.49 (app tt, $J = 6.31, 8.60$ Hz, 1H), 7.33-28 (m, 2H), 7.10-6.97 (m, 5H), 5.17 (s, 2H). ES-HRMS m/z 437.0083 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{12}\text{BrF}_3\text{N}_2\text{O}_2$ requires 437.0107).

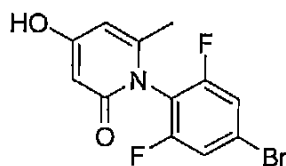
30

Ex. 312



5 3-bromo-1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 1-(4-bromo-2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one .

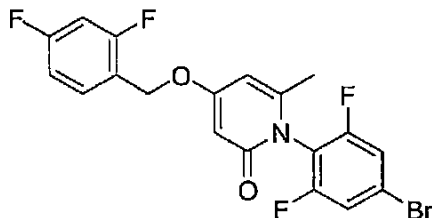


10

4-Hydroxy-6-methyl-2-pyrone (30.0 g, 238 mmol) and 4-bromo-2,6-difluoroaniline (49.5 g, 238 mmol) were suspended in 50 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked, round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 80°C. The flask was placed in an ice bath and about 25 ml of toluene was added and stirred. After about 10 minutes, a precipitate formed. The precipitate was filtered and washed 3 times with toluene, 3 times with hot water to remove excess pyrone, and dried in vacuo to give a tan solid (22.1 g, 29%). ¹H NMR (400 MHz, DMSO-d₆) δ 11.00 (br s, 1H), 7.71 (d, J = 6.98 Hz, 2H), 5.97 (t, J = 0.88 Hz, 1H), 5.55 (d, J = 2.28 Hz, 1H), 1.91 (s, 3H). LC/MS, t_r = 1.96 minutes (5 to 95% acetonitrile/water over 5

minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 316 (M+H). ES-HRMS m/z 315.9779 (M+H calcd for $C_{12}H_8BrF_2NO_2$ requires 315.9779).

5 Step 2: Preparation of 1-(4-bromo-2,6-difluorophenyl)-4-
[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one .

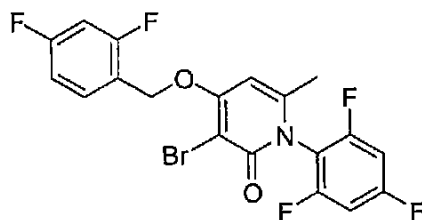


1-((4-bromo-2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (from Step 1) (5.0 g, 15.8 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (2.23 ml, 17.4 mmol) and K₂CO₃ (3.27 g, 23.7 mmol) in 50 ml of dimethylformamide. After stirring overnight, the reaction was poured quickly into 900 ml of cold water. The resulting precipitate was filtered and washed with water and hexane. The product was purified using a Biotage silica chromatography system using 20% ethyl acetate/hexanes to give a beige solid (4.32 g, 62%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 (app q, *J* = 6.31 Hz, 1H), 7.25 (dd, *J* = 8.33, 1.74 Hz, 2H), 6.91 (dt, *J* = 9.2, 0.8 Hz, 1H), 6.86 (dt, *J* = 9.2, 0.8 Hz, 1H), 5.95 (d, *J* = 2.56 Hz, 1H), 5.92 (dd, *J* = 2.56, 0.94 Hz, 1H), 5.01 (s, 2H), 1.98 (s, 3H). LC/MS, *t_r* = 3.04 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS *m/z* 442 (M+H). ES-HRMS *m/z* 442.0057 (M+H calcd for C₁₉H₁₃BrF₄NO₂ requires 442.0060).

Step 3: Preparation of the title compound . 1-(4-bromo-2,6-difluorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-

2(1H)-one (from Step 2) (500 mg, 1.13 mmol) was stirred at room temperature with N-bromosuccinimide (221 mg, 1.24 mmol) in 5 ml of CH₂Cl₂ for 1.5 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried in vacuo to yield a white solid (478 mg, 92%). ¹H NMR (300 MHz, CDCl₃) δ 7.62 (app q, J = 6.64 Hz, 1H), 7.31 (d, J = 6.85 Hz, 2H), 7.01 (app t, J = 8.36 Hz, 1H), 6.96 (dt, J = 9.46, 2.21 Hz, 1H), 6.19 (s, 1H), 5.30 (s, 2H), 2.10 (s, 3H); LC/MS, t_r = 3.17 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 520 (M+H). ES-HRMS m/z 521.9134 (M+H calcd for C₁₉H₁₁Br₂F₄NO₂ requires 521.9146).

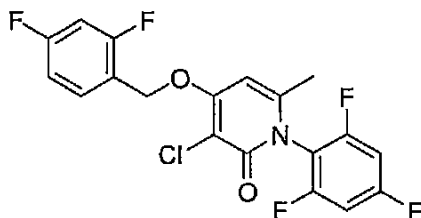
Ex. 313



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

The title compound was produced essentially as in Example 313, using 2,4,6-trifluoroaniline instead of 4-bromo-2,6-difluoroaniline. ¹H NMR (300 MHz, CDCl₃) δ 7.62 (app q, J = 7.79 Hz, 1H), 7.01 (app dt, J = 8.26, 2.01 Hz, 1H), 6.95 - 6.85 (m, 3H), 6.19 (s, 1H), 5.30 (s, 2H), 2.11 (s, 3H); LC/MS, t_r = 2.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 460 (M+H). ES-HRMS m/z 459.9954 (M+H calcd for C₁₉H₁₁BrF₅NO₂ requires 459.9966).

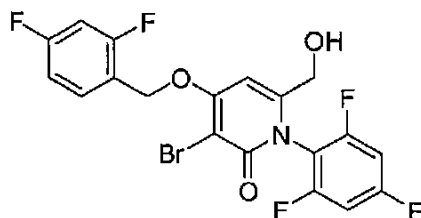
Ex. 314



5 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

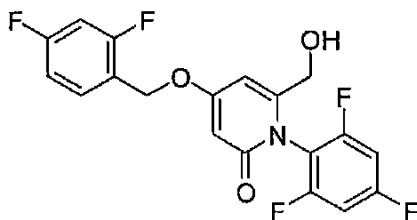
4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (350 mg, 0.92 mmol) was
 10 refluxed with N-chlorosuccinimide (147 mg, 1.1 mmol) and dichloroacetic acid (0.038 ml, 0.46 mmol) in 5 ml of CH₂Cl₂ overnight. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried in vacuo to yield a white solid (217 mg, 57%). ¹H
 15 NMR (300 MHz, CDCl₃) δ 7.60 (app q, J = 7.75 Hz, 1H), 7.00 (app dt, J = 8.23, 2.05 Hz, 1H), 6.93 – 6.86 (m, 3H), 6.22 (s, 1H), 5.30 (s, 2H), 2.12 (s, 3H); LC/MS, t_r = 2.78 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 416 (M+H). ES-HRMS m/z 416.0472 (M+H calcd
 20 for C₁₉H₁₁ClF₅NO₂ requires 416.0471).

Ex. 315



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one

- 5 Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one .

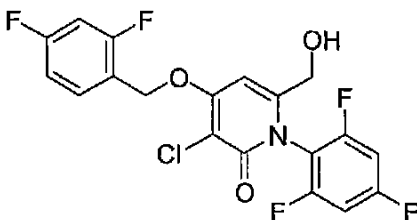


- 4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (9.0 g, 23.6 mmol) was
 10 heated to 135°C overnight with SeO₂ (13.1 g, 118 mmol) in 75 ml of 1,4-dioxane in a 350 ml sealed glass pressure vessel. The reaction mixture was cooled and placed on a plug of silica gel and washed with 5% methanol in CH₂Cl₂. The filtrate was evaporated and the resulting solid was washed with diethyl
 15 ether and dissolved in hot ethyl acetate. The insoluble Se salts were filtered off and the organic layer was evaporated. 7.01g (17.6 mmol) of a 3:1 ratio of aldehyde to desired alcohol was isolated. The mixture was stirred with NaBH₄ (802 mg, 21.2 mmol) in 30 ml of methanol at room temperature for 1
 20 hour. The reaction was evaporated and CH₂Cl₂ and acetonitrile were used to dissolve the bulk of the solid. The remaining insoluble solid was filtered off. The organic layer was washed 3 times with NH₄Cl, dried over MgSO₄ and evaporated. The resulting solid was washed 3 times with diethyl ether and
 25 dried *in vacuo* to yield a light orange solid (4.35 g, 46%). ¹H NMR (300 MHz, DMSO-d₆) δ 7.68 (app q, *J* = 7.92 Hz, 1H), 7.47 (app t, *J* = 8.57 Hz, 2H), 7.35 (dt, *J* = 9.87, 2.42 Hz, 1H), 7.18 (dt, *J* = 8.31, 1.71 Hz, 1H), 6.21 (d, *J* = 2.42 Hz, 1H), 6.07 (d, *J* = 2.62 Hz, 1H), 5.67 (br s, 1H), 5.18 (s, 2H), 3.98

(s, 2H); LC/MS, t_r = 2.31 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 398 (M+H).

5 Step 2: Preparation of the title compound . 4-[(2,4-Difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (from step 1) (2.1 g, 5.28 mmol) was stirred at room temperature with N-bromosuccinimide (1.13 g, 6.34 mmol) in 5 ml CH_2Cl_2 for 2 hours. The reaction
10 was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (1.35 g, 54%). ^1H NMR (300 MHz, CD_3OD) δ 7.69 (app q, J = 6.65 Hz, 1H), 7.20 (app t, J = 8.36 Hz, 2H), 7.09 (app t, J = 8.46 Hz, 2H), 6.88 (s, 1H), 5.46 (s, 2H),
15 4.21 (s, 2H); LC/MS, t_r = 2.48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 476 (M+H). ES-HRMS m/z 475.9907 (M+H calcd for $\text{C}_{19}\text{H}_{11}\text{BrF}_5\text{NO}_3$ requires 475.9915).

20 Ex. 316

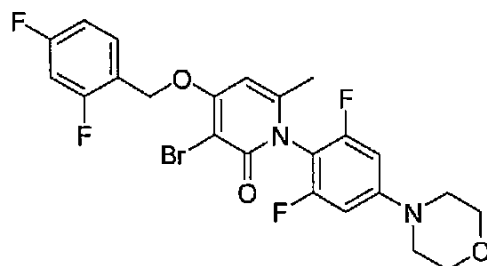


3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-
25 (2,4,6-trifluorophenyl)pyridin-2(1H)-one

4-[(2,4-Difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (2.1 g, 5.28 mmol) was

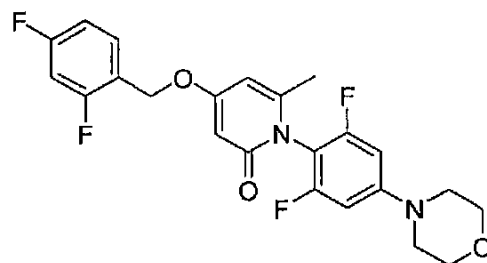
refluxed with *N*-chlorosuccinimide (846 mg, 6.34 mmol) and dichloroacetic acid (0.87 ml, 10.56 mmol) in 5 ml CH₂Cl₂ overnight. The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with diethyl ether to
5 obtain a solid. The solid was washed 4 times with acetonitrile. Chromatography was done using a Biotage silica gel system with 60% ethyl acetate/hexanes. The recovery was poor from the column to give a white solid (109 mg, 5%). ¹H NMR (300 MHz, CD₃OD) δ 7.67 (app q, *J* = 7.85 Hz, 1H), 7.24 -
10 7.06 (m, 4H), 6.90 (s, 1H), 5.45 (s, 2H), 4.22 (s, 2H); LC/MS, *t_r* = 2.71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 432 (M+H). ES-HRMS *m/z* 432.0413 (M+H calcd for C₁₉H₁₁ClF₅NO₃ requires 432.0420).

15 Ex. 317



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-
20 morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one

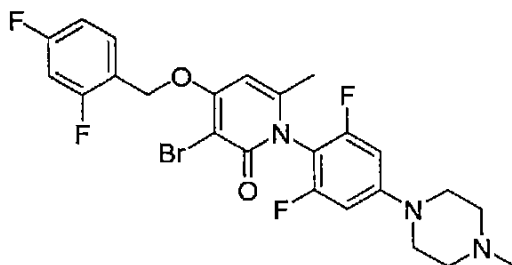
Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one .



4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (870 mg, 2.28 mmol) was heated to 100°C with K₂CO₃ (630 mg, 4.56 mmol) in 5 ml of morpholine for 36 hours. The reaction was added to 200 ml of cold water and the resulting solid was washed with water and 50:50 diethyl ether/hexanes and dried *in vacuo* to give a beige solid (738 mg, 72%). ¹H NMR (400 MHz, CDCl₃) δ 7.41 (*app* q, *J* = 7.70 Hz, 1H), 6.93 - 6.85 (m, 2H), 6.49 (d, *J* = 10.47 Hz, 2H), 5.96 (d, *J* = 2.41 Hz, 1H), 5.89 (d, *J* = 1.75 Hz, 1H), 5.00 (s, 2H), 3.83 (t, *J* = 4.83 Hz, 4H), 3.19 (t, *J* = 4.84 Hz, 4H), 1.99 (s, 3H); LC/MS, *t_r* = 3.09 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 449 (M+H). ES-HR/MS *m/z* 449.1485 (M+H calcd for C₂₃H₂₀F₄N₂O₃ requires 449.1483).

Step 2: Preparation of the title compound. 4-[(2,4-Difluorobenzyl)oxy]-1-(2,6-difluoro-4-morpholin-4-ylphenyl)-6-methylpyridin-2(1H)-one (from step 1) (500 mg, 1.12 mmol) was stirred at room temperature with *N*-bromosuccinimide (236 mg, 1.33 mmol) in 5 ml of CH₂Cl₂ for 2 hours. The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with diethyl ether to obtain a solid. The solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (171 mg, 29%). ¹H NMR (400 MHz, CDCl₃) δ 7.58 (*app* q, *J* = 7.74 Hz, 1H), 6.96 (*app* t, *J* = 8.39 Hz, 1H), 6.86 (dt, *J* = 9.46, 2.28 Hz, 1H), 6.50 (d, *J* = 10.74 Hz, 2H), 6.09 (s, 1H), 5.24 (s, 2H), 3.84 (t, *J* = 4.84 Hz, 4H), 3.20 (t, *J* = 4.83 Hz, 4H), 2.07 (s, 3H); LC/MS, *t_r* = 3.18 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 527 (M+H). ES-HRMS *m/z* 527.0570 (M+H calcd for C₂₃H₁₉BrF₄N₂O₃ requires 527.0588).

Ex. 318



5 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

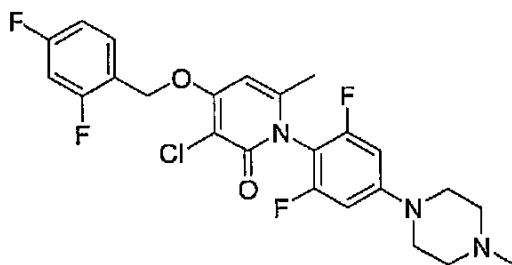
10

The title compound was prepared essentially as in Example 317, using 1-methylpiperazine instead of morpholine. ¹H NMR (400 MHz, CDCl₃) δ 7.57 (app q, *J* = 7.79 Hz, 1H), 6.96 (dt, *J* = 8.19, 1.88 Hz, 1H), 6.86 (app dt, *J* = 9.44, 2.48 Hz, 1H), 6.52 (d, *J* = 10.61 Hz, 2H), 6.14 (s, 1H), 5.24 (s, 2H), 3.72 (br s, 4H), 3.51 (d, *J* = 11.27 Hz, 2H), 3.07 (br s, 2H), 2.85 (d, *J* = 4.29 Hz, 3H), 2.06 (s, 3H); LC/MS, *t_r* = 2.50 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 540 (M+H). ES-HRMS *m/z* 540.0930 (M+H calcd for C₂₄H₂₂BrF₄N₃O₂ requires 540.0904).

15

20

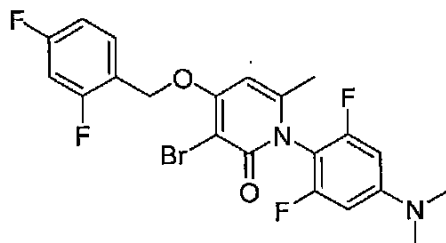
Ex. 320



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one

4-[(2,4-Difluorobenzyl)oxy]-1-[2,6-difluoro-4-(4-methylpiperazin-1-yl)phenyl]-6-methylpyridin-2(1H)-one (1.3 g, 2.82 mmol) was stirred at reflux with *N*-chlorosuccinimide (451 mg, 3.38 mmol) and dichloroacetic acid (0.17 ml, 1.41 mmol) in 6 ml CH₂Cl₂ overnight. LC-MS showed 33% completion. More *N*-chlorosuccinimide (271 mg, 2.23 mmol) was added and refluxed overnight. The reaction was evaporated on a rotary evaporator and the resulting oil was triturated with ethyl acetate to obtain a solid. The solid was washed 4 times with ethyl acetate and with diethyl ether and dried in vacuo to obtain a white solid (606 mg, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.66 (br q, *J* = 7.74 Hz, 1H), 7.33 (br t, *J* = 9.00 Hz, 1H), 7.16 (br t, *J* = 7.65 Hz, 1H), 6.96 (d, *J* = 11.81 Hz, 2H), 6.79 (s, 1H), 5.33 (s, 2H), 3.61 (br m, 4H), 3.25 (br m, 4H), 3.21 (br s, 3H), 2.04 (s, 3H); LC/MS, *t*_r = 2.45 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 496 (M+H). ES-HRMS *m/z* 496.1400 (M+H calcd for C₂₄H₂₂ClF₄N₃O₂ requires 496.1409).

Example 321

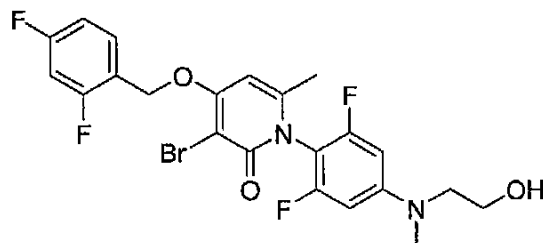


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(dimethylamino)-2,6-difluorophenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared essentially as described in Example 317, using dimethylamine instead of morpholine. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (q, *J* = 7.74 Hz, 1H), 6.95 (dt, *J* = 8.32, 1.61 Hz, 1H), 6.85 (app dt, *J* = 9.54, 2.41 Hz, 1H), 6.27 (d, *J* = 11.01 Hz, 2H), 6.08 (s, 1H), 5.23 (s, 2H), 2.98 (s, 3H), 2.07 (s, 3H); LC/MS, *t_r* = 3.35 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 485 (M+H). ES-HRMS *m/z* 485.0447 (M+H calcd for C₂₁H₁₇BrF₄N₂O₂ requires 485.0482).

10

Example 322



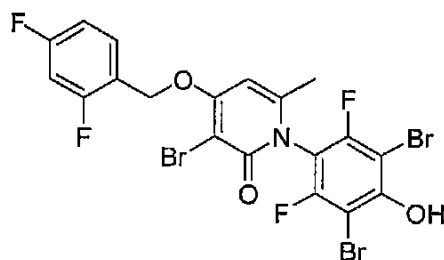
15

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-[(2-hydroxyethyl)(methyl)amino]phenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared essentially as in Example 317, using 2-(methylamino)ethanol instead of morpholine.

¹H NMR (400 MHz, CDCl₃) δ 7.58 (q, *J* = 7.74 Hz, 1H), 6.95 (dt, *J* = 8.24, 1.66 Hz, 1H), 6.85 (app dt, *J* = 9.49, 2.37 Hz, 1H), 6.35 (d, *J* = 11.01 Hz, 2H), 6.10 (s, 1H), 5.23 (s, 2H), 3.77 (t, *J* = 5.77 Hz, 2H), 3.45 (t, *J* = 5.78 Hz, 2H), 2.99 (s, 3H), 2.08 (s, 3H); LC/MS, *t_r* = 2.96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 515 (M+H). ES-HRMS *m/z* 515.0576 (M+H calcd for C₂₂H₁₉BrF₄N₂O₃ requires 515.0588).

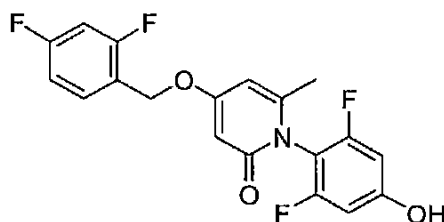
Example 323



5 3-bromo-1-(3,5-dibromo-2,6-difluoro-4-hydroxyphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one .

10



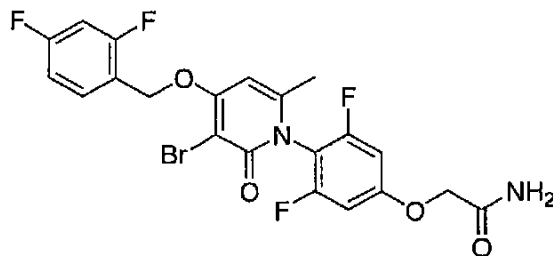
4-[(2,4-Difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (step 2 above) (10.0 g, 26.2 mmol) was heated to 45°C with KOSiMe₃ (10.08 g, 78.6 mmol) in
 15 50 ml of tetrahydrofuran for 4 days. The reaction was diluted with 30 ml of ethyl acetate and washed with 1N HCl and water, dried over MgSO₄, and evaporated to give an orange solid. The solid was stirred in hot 60% ethyl acetate/hexanes and filtered to give a white solid, which was dried *in vacuo* to
 20 obtain a white solid (3.79 g, 38%). The filtrate was found to contain a mixture of desired product and the ortho substituted regioisomer. ¹H NMR (400 MHz, CDCl₃) δ 7.42 (*app* q, *J* = 7.70 Hz, 1H), 6.95 – 6.83 (m, 2H), 6.34 (d, *J* = 9.40 Hz, 2H), 6.05 (*app* s, 2H), 5.06 (s, 2H), 2.01 (s, 3H); LC/MS, *t_r* = 2.80
 25 minutes (5 to 95% acetonitrile/water over 5 minutes at 1

ml/min, at 254 nm, at 50°C), ES-MS m/z 380 (M+H). ES-HRMS m/z 380.0926 (M+H calcd for $C_{19}H_{13}F_4NO_3$ requires 380.0904).

Step 2: Preparation of the title compound . 4-[(2,4-

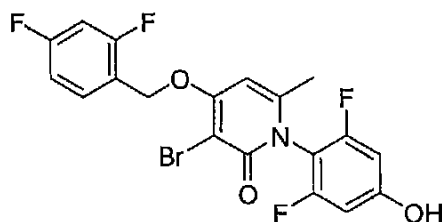
5 Difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one (from step 1) (3.73 g, 8.14 mmol) was stirred as a suspension at room temperature with *N*-bromosuccinimide (1.52 g, 8.55 mmol) in 30 ml CH_2Cl_2 overnight. LC-MS showed a 60% starting material. The solid was filtered
10 off, dissolved in 30 ml of CH_2Cl_2 /*N,N*-dimethylformamide and stirred with more *N*-bromosuccinimide (0.76 g, 4.28 mmol) overnight. LC-MS showed the tri-brominated product as the major product. The reaction was poured into water and extracted with *n*-butanol. The combined organic layers were
15 evaporated on a rotary evaporator and the resulting solid was washed with diethyl ether and dried *in vacuo* to yield a white solid (873 mg, 17%). 1H NMR (400 MHz, $CDCl_3$) δ 7.67 (app q, J = 7.80 Hz, 1H), 7.32 (dt, J = 4.86, 2.11 Hz, 1H), 7.16 (dt, J = 8.48, 1.84 Hz, 1H), 6.79 (s, 1H), 5.35 (s, 2H), 2.08 (s,
20 3H); LC/MS, t_r = 3.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 616 (M+H). ES-HRMS m/z 615.8234 (M+H calcd for $C_{19}H_{10}Br_3F_4NO_3$ requires 615.8200).

25 Example 324



2-{4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-difluorophenoxy}acetamide

Step 1: Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one .

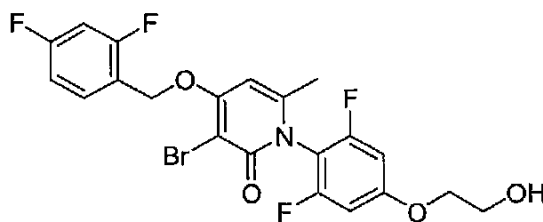


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2,4,6-trifluorophenyl)pyridin-2(1H)-one (above) (7.5 g, 16.3 mmol) was heated to 45°C with KOSiMe₃ (10.08 g, 78.6 mmol) in 50 ml of tetrahydrofuran for 48 hours. The reaction was diluted with 30 ml of ethyl acetate and washed with 1N HCl and water, dried over MgSO₄, and evaporated to give a black oil. The oil was dissolved in ethyl acetate. A precipitate formed upon standing, which was filtered, washed with ethyl acetate and dried in vacuo to obtain a white solid (2.80 g, 37%). The filtrate showed the presence of desired product and the ortho substituted regioisomer. ¹H NMR (400 MHz, DMSO-d₆) δ 7.66 (q, J = 7.92 Hz, 1H), 7.32 (dt, J = 8.77, 2.19 Hz, 1H), 7.15 (m, 1H), 6.73 (s, 1H), 6.67 (d, J = 9.66 Hz, 2H), 5.33 (s, 2H), 2.03 (s, 3H); LC/MS, t_r = 2.92 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 458 (M+H). ES-HRMS m/z 457.9995 (M+H calcd for C₁₉H₁₂BrF₄NO₃ requires 458.0009).

Step 2: Preparation of the title compound . 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluoro-4-hydroxyphenyl)-6-methylpyridin-2(1H)-one (from step 1) (500 mg, 1.09 mmol) was

stirred briskly with 2-bromoacetamide (196 mg, 1.43 mmol) and K_2CO_3 (282 mg, 2.05 mmol) in 5 ml of *N,N*-dimethylformamide at room temperature for 24 hours. The reaction was poured quickly into cold water and the resulting solid was filtered, washed with water, acetonitrile, and diethyl ether, and dried in vacuo to give a white solid (289 mg, 51%). 1H NMR (400 MHz, DMSO- d_6) δ 7.66 (q, J = 7.92 Hz, 1H), 7.61 (br s, 1H), 7.45 (br s, 1H), 7.33 (dt, J = 10.07, 2.15 Hz, 1H), 7.16 (dt, J = 8.53, 1.88 Hz, 1H), 6.99 (d, J = 9.54 Hz, 2H), 6.76 (s, 1H), 5.34 (s, 2H), 2.03 (s, 3H); LC/MS, t_r = 2.70 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 515 (M+H). ES-HRMS m/z 515.0245 (M+H calcd for $C_{21}H_{15}BrF_4N_2O_4$ requires 515.0224).

Example 325



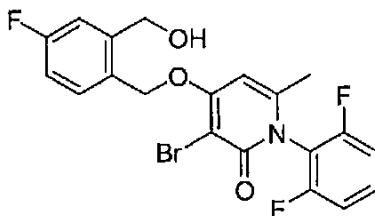
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2,6-difluoro-4-(2-hydroxyethoxy)phenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 324. 1H NMR (400 MHz, DMSO- d_6) δ 7.66 (q, J = 7.92 Hz, 1H), 7.33 (dt, J = 10.04, 2.19 Hz, 1H), 7.17 (dt, J = 8.68, 1.84 Hz, 1H), 6.99 (d, J = 9.67 Hz, 2H), 6.75 (s, 1H), 5.34 (s, 2H), 4.92 (t, J = 4.86 Hz, 1H), 4.07 (t, J = 4.77 Hz, 2H), 3.70 (t, J = 4.83 Hz, 2H), 2.03 (s, 3H); LC/MS, t_r = 2.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 502 (M+H).

ES-HRMS m/z 502.0291 (M+H calcd for $C_{21}H_{16}BrF_4NO_4$ requires 502.0272).

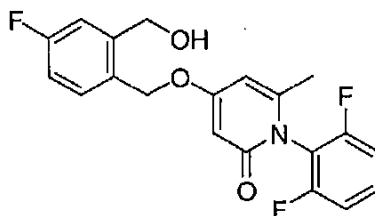
Example 326

5



3-bromo-1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one

10 Step 1: Preparation of 1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one .



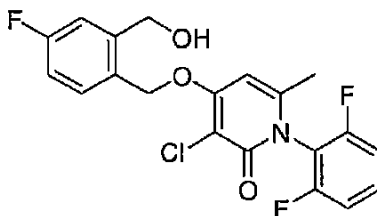
1-(2,6-Difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

(step 1) (3.0 g, 12.65 mmol) was dissolved in *N,N*-dimethylformamide and cooled to 0°C. Triphenylphosphine (3.98 g, 15.18 mmol) and diethyl azodicarboxylate (2.39 ml, 15.18 mmol) were added and stirred for 10 minutes. 1,2-Bis(hydroxymethyl)-4-fluorobenzene (2.57 g, 16.44 mmol) was added and stirred at 0°C for 1 hour, then allowed to warm to room temperature and stirred overnight. LC-MS showed only 1 product, not a mixture of regioisomers, as expected. The reaction was added to water and extracted 3 times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and evaporated. A Biotage silica column was done using 60% ethyl acetate/hexanes as an eluent. Desired product, with a substantial impurity was obtained. Another Biotage silica

column was ran using 30% ethyl acetate/hexanes to obtain pure product. The resulting oil was triturated with diethyl ether to obtain a white solid (720 mg, 15%). ^1H NMR (300 MHz, CDCl_3) δ 7.51 - 7.39 (m, 2H), 7.26 (dd, J = 9.62, 2.51 Hz, 1H), 7.13 - 7.01 (m, 3H), 6.03 (d, J = 2.42 Hz, 1H), 5.96 (d, J = 2.41 Hz, 1H), 5.06 (s, 2H), 4.73 (s, 2H), 2.81 (br s, 1H), 2.02 (s, 3H); LC/MS, t_r = 2.37 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 376 (M+H). ES-HR/MS m/z 376.1181 (M+H calcd for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{NO}_3$ requires 376.1155). Identity of the positional isomer was determined from hmbc, 2-D NMR experiments using H to C 2- and 3- bond coupling.

Step 2: Preparation of the title compound . 1-(2,6-Difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one (from step 1) (350 mg, 0.93 mmol) was stirred at room temperature with *N*-bromosuccinimide (199 mg, 1.12 mmol) in 1.5 ml CH_2Cl_2 for 1.5 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (197 mg, 47%). ^1H NMR (300 MHz, CDCl_3) δ 7.53 - 7.43 (m, 2H), 7.25 (dd, J = 9.46, 2.62 Hz, 1H), 7.11 - 7.03 (m, 3H), 6.25 (s, 1H), 5.31 (s, 2H), 4.81 (s, 2H), 2.28 (br s, 1H), 2.10 (s, 3H); LC/MS, t_r = 2.38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 454 (M+H). ES-HRMS m/z 454.0247 (M+H calcd for $\text{C}_{20}\text{H}_{15}\text{BrF}_3\text{NO}_3$ requires 454.0260).

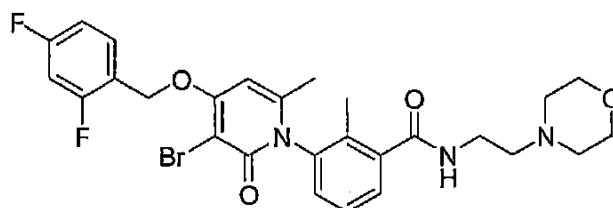
Example 327



3-chloro-1-(2,6-difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one

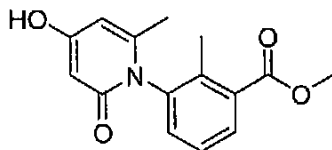
5 1-(2,6-Difluorophenyl)-4-{[4-fluoro-2-(hydroxymethyl)benzyl]oxy}-6-methylpyridin-2(1H)-one (step 1 above) (275 mg, 0.73 mmol) was stirred at reflux with *N*-chlorosuccinimide (117 mg, 0.88 mmol) and dichloroacetic acid (0.03 ml, 0.36 mmol) in 1.5 ml CH₂Cl₂ overnight. The reaction
10 was evaporated on a rotary evaporator and the resulting solid was washed 4 times with ethyl acetate and with diethyl ether and dried *in vacuo* to obtain a white solid (65.5 mg, 22%). ¹H NMR (300 MHz, CDCl₃) δ 7.52 - 7.43 (m, 2H), 7.26 (dd, *J* = 9.38, 2.52 Hz, 1H), 7.12 - 7.04 (m, 3H), 6.27 (s, 1H), 5.32 (s, 2H),
15 4.82 (s, 2H), 2.29 (br s, 1H), 2.11 (s, 3H); LC/MS, *t_r* = 2.32 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 410 (M+H). ES-HRMS *m/z* 410.0755 (M+H calcd for C₂₀H₁₅ClF₃NO₃ requires 410.0765).

20 Example 328



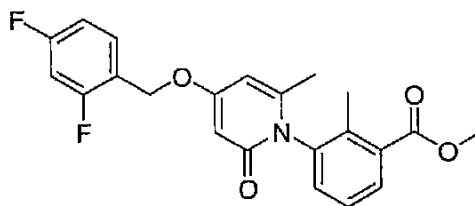
3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methyl-N-(2-morpholin-4-ylethyl)benzamide

25 Step 1: Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-2-methylbenzoate .



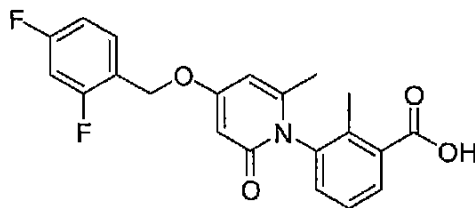
4-Hydroxy-6-methyl-2-pyrone (72.6 g, 576 mmol) and methyl-3-amino-2-methylbenzoate (100 g, 605 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 500 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 80°C. The flask was placed in an ice bath and about 300 ml of toluene was added and stirred. After about 30 minutes, a precipitate formed. The precipitate was filtered and washed 3 times with toluene, 3 times with hot water to remove excess pyrone, and dried in vacuo to give a tan solid (44.6 g, 28% yield). ¹H NMR (400 MHz, DMSO-d₆) δ 10.66 (br s, 1H), 7.80 (dd, *J* = 7.72, 1.28 Hz, 1H), 7.33 (dd, *J* = 7.78, 1.34 Hz, 1H), 5.91 (dd, *J* = 2.41, 0.69 Hz, 1H), 5.55 (d, *J* = 2.42 Hz, 1H), 3.82 (s, 3H), 2.06 (s, 3H), 1.73 (s, 3H); LC/MS, *t_r* = 1.85 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 274 (M+H). ES-HRMS *m/z* 274.1078 (M+H calcd for C₁₅H₁₅NO₄ requires 274.1074).

Step 2: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoate.



Methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-2-methylbenzoate (from Step 1) (42.0 g, 154 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (19.7 ml, 154 mmol) and K_2CO_3 (31.8 g, 231 mmol) in 250 ml of *N,N*-dimethylformamide. After stirring overnight, the reaction was poured into 1 L of cold water. The solution was extracted 3 times with ethyl acetate and the organic layers were dried over $MgSO_4$, and evaporated. The product was carried on to the next step as a crude oil (60.4 g, 85%). 1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.85, 1.28 Hz, 1H), 7.45 - 7.34 (m, 2H), 7.27 - 7.23 (m, 1H), 6.94 - 6.84 (m, 2H), 5.98 (d, J = 2.68 Hz, 1H), 5.92 (dd, J = 2.69, 0.81 Hz, 1H), 5.01 (s, 2H), 3.88 (s, 3H), 2.28 (s, 3H), 1.81 (s, 3H); LC/MS, t_r = 2.96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 400 ($M+H$). ES-HRMS m/z 400.1341 ($M+H$ calcd for $C_{22}H_{19}F_2NO_4$ requires 400.1355).

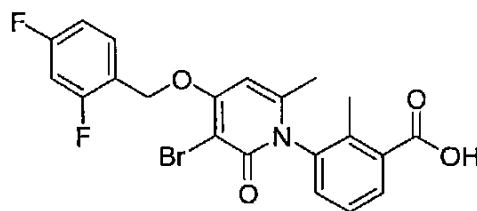
Step 3: Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid.



Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoate (from Step 2) (60.0 mg, 150 mmol) was stirred with 2.5 N NaOH (120 ml, 300 mmol) in 375 ml of tetrahydrofuran and 75 ml of water at room temperature overnight. The reaction was acidified with 1 N HCl, 350 ml of water was added and the solution was extracted 3 times with ethyl acetate. The combined organic layers were dried over

MgSO₄, filtered and evaporated. The resulting solid was filtered, washed with ethyl acetate and dried *in vacuo* to yield a white solid 33.8 g, 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.98 (dd, *J* = 7.92, 1.20 Hz, 1H), 7.43 (app q, *J* = 7.70 Hz, 1H), 7.38 (t, *J* = 7.72 Hz, 1H), 7.35 (dd, *J* = 7.81, 1.21 Hz, 1H), 6.92 – 6.84 (m, 2H), 6.17 (d, *J* = 2.56 Hz, 1H), 6.00 (dd, *J* = 2.55, 0.81 Hz, 1H), 5.05 (s, 2H), 2.30 (s, 3H), 1.84 (s, 3H); LC/MS, *t_r* = 2.61 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 386 (M+H). ES-HR/MS *m/z* 386.1228 (M+H calcd for C₂₁H₁₇F₂NO₄ requires 386.1198).

Step 4: Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid.



3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (from Step 3) (23.0 g, 59.7 mmol) was stirred at room temperature with *N*-bromosuccinimide (12.74 g, 71.6 mmol) in 120 ml of CH₂Cl₂ for 2 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in acetonitrile for 1 hour, washed 7 times with acetonitrile and dried *in vacuo* to yield a white solid (19.14 g, 69%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.87 (dd, *J* = 7.52, 1.61 Hz, 1H), 7.67 (app q, *J* = 7.92 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.33 (dt, *J* = 9.87, 2.54 Hz, 1H), 7.17 (dt, *J* = 8.50, 1.67 Hz, 1H), 6.71 (s, 1H), 5.32 (s, 2H), 2.08 (s, 3H), 1.86 (s, 3H);

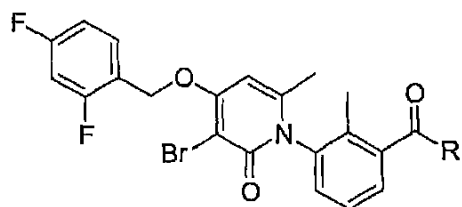
LC/MS, t_r = 2.69 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 464 (M+H). ES-HRMS m/z 464.0284 (M+H calcd for $C_{21}H_{16}BrF_2NO_4$ requires 464.0304).

5

Step 5: Preparation of the title compound. 3-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (from Step 4 above) (500 mg, 1.08 mmol) was dissolved in 5 ml of CH_2Cl_2 . 4-(2-Aminoethyl)morpholine (170 μ l, 1.29 mmol) was added, followed, in order, by EDCI (247 mg, 1.29 mmol), 1-hydroxybenzotriazole (174 mg, 1.29 mmol) and triethylamine (301 μ l, 2.16 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl and extracted 3 times with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and evaporated. The resulting oil was triturated with diethyl ether/hexane to obtain a solid, which was dried in vacuo to give a white solid (472 mg, 76%). 1H NMR (400 MHz, $DMSO-d_6$) δ 7.64 (app q, J = 7.79 Hz, 1H), 7.47 (dd, J = 7.65, 1.01 Hz, 1H), 7.39 (t, J = 7.75 Hz, 1H), 7.17 (dd, J = 7.65, 0.81 Hz, 1H), 7.01 (dt, J = 8.26, 1.61 Hz, 1H), 6.91 (dt, J = 9.42, 2.32 Hz, 1H), 6.49 (t, J = 5.04 Hz, 1H), 6.18 (s, 1H), 5.30 (s, 2H), 3.73 (t, J = 4.53 Hz, 4H), 3.68 - 3.47 (m, 2H), 2.59 (t, J = 5.94 Hz, 2H), 2.51 (t, J = 4.33 Hz, 4H), 2.15 (s, 3H), 1.98 (s, 3H); LC/MS, t_r = 2.27 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 576 (M+H). ES-HRMS m/z 576.1313 (M+H calcd for $C_{27}H_{28}BrF_2N_3O_4$ requires 576.1304).

Examples 329-337

The following compounds are prepared essentially according to the procedure set forth for Example 328:



Example No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 329	-NHCH ₂ CH ₂ OCH ₃	C ₂₄ H ₂₂ BrF ₂ N ₂ O ₄	521.0882	521.0906
Ex. 330	-N(CH ₃) ₂	C ₂₃ H ₂₀ BrF ₂ N ₂ O ₃	491.0776	491.0752
Ex. 331	-NHCH ₂ CH ₂ OH	C ₂₃ H ₂₀ BrF ₂ N ₂ O ₄	507.0726	507.0689
Ex. 332	-NHCH ₃	C ₂₂ H ₁₈ BrF ₂ N ₂ O ₃	477.0620	477.0585
Ex. 333	-N(CH ₃)CH ₂ CH ₂ OH	C ₂₄ H ₂₂ BrF ₂ N ₂ O ₄	521.0882	521.0890
Ex. 334	4-methylpiperazin-1-yl	C ₂₆ H ₂₅ BrF ₂ N ₃ O ₃	546.1198	546.1187
Ex. 335	morpholin-4-yl	C ₂₅ H ₂₂ BrF ₂ N ₂ O ₄	533.0882	533.0856
Ex. 336	-N(CH ₃)CH ₂ CH ₂ OCH ₃	C ₂₅ H ₂₄ BrF ₂ N ₂ O ₄	535.1039	535.1055
Ex. 337	-NH ₂	C ₂₁ H ₁₆ BrF ₂ N ₂ O ₃	463.0463	463.0492

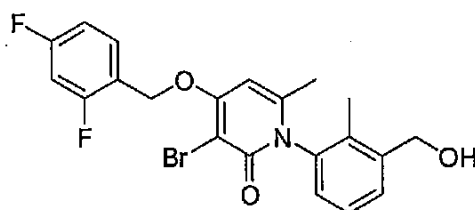
NMR characterization of compounds of Examples 329-337

5

Example No.	NMR Data
Ex. 329	¹ H NMR (400 MHz, CDCl ₃) δ 7.59 (app q, J = 7.79 Hz, 1H), 7.47 (dd, J = 7.65, 1.08 Hz, 1H), 7.34 (t, J = 7.72 Hz, 1H), 7.12 (dd, J = 7.78, 0.94 Hz, 1H), 6.96 (app dt, J = 7.92, 2.27 Hz, 1H), 6.87 (dt, J = 9.46, 2.55 Hz, 1H), 6.29 (m, 1H), 6.12 (s, 1H), 5.25 (s, 2H), 3.73 - 3.65 (m, 1H), 3.56 - 3.48 (m, 3H), 3.35 (d, J = 3.09 Hz, 3H), 2.09 (s, 3H), 1.93 (s, 3H)
Ex. 330	¹ H NMR (400 MHz, CDCl ₃) δ 7.59 (app q, J = 7.79 Hz, 1H), 7.34 (t, J = 7.66 Hz, 1H), 7.28 (dd, J = 7.66, 1.21 Hz, 1H), 7.07 (dd, J = 7.65, 1.08 Hz, 1H), 6.96 (app dt, J = 8.52, 2.02 Hz, 1H), 6.87 (dt, J = 9.46, 2.55 Hz, 1H), 6.29 (m, 1H), 6.12 (s, 1H), 5.25 (s, 2H), 3.11 (s, 3H), 2.82 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H)
Ex. 331	¹ H NMR (400 MHz, CDCl ₃) δ 7.59 (app q, J = 7.74 Hz, 1H), 7.46 (d, J = 6.71 Hz, 1H), 7.32 (t, J = 7.72 Hz, 1H), 7.07 (d, J = 6.85 Hz, 1H), 6.98 (m, 2H), 6.87 (dt, J = 9.47, 2.41 Hz, 1H),

	6.15 (s, 1H), 5.26 (s, 2H), 3.71 (t, $J = 4.97$ Hz, 2H), 3.60 - 3.45 (m, 2H), 2.06 (s, 3H), 1.95 (s, 3H)
Ex. 332	^1H NMR (400 MHz, CDCl_3) δ 7.59 (app q, $J = 7.79$ Hz, 1H), 7.42 (dd, $J = 7.66$, 0.94 Hz, 1H), 7.31 (t, $J = 7.72$ Hz, 1H), 7.09 (dd, $J = 7.79$, 0.94 Hz, 1H), 6.96 (app dt, $J = 8.26$, 1.61 Hz, 1H), 6.87 (dt, $J = 9.44$, 2.49 Hz, 1H), 6.12 (s, 1H), 5.25 (s, 2H), 2.96 (d, $J = 4.83$ Hz, 3H), 2.07 (s, 3H), 1.93 (s, 3H)
Ex. 333	^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.73 (q, $J = 7.92$ Hz, 1H), 7.44 - 7.20 (m, 5H), 6.75 (s, 1H), 5.37 (s, 2H), 4.83 (br s, 1H), 3.65 (br s, 2H), 3.45 - 3.33 (m, 2H), 2.81 (s, 3H), 1.93 (d, $J = 3.42$ Hz, 3H), 1.85 (d, $J = 8.06$ Hz, 3H)
Ex. 334	^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.67 (app q, $J = 7.92$ Hz, 1H), 7.40 (t, $J = 7.78$ Hz, 1H), 7.34 (dt, $J = 9.87$, 2.55 Hz, 1H), 7.27 (d, $J = 7.52$ Hz, 1H), 7.24 (d, $J = 7.79$ Hz, 1H), 7.17 (dt, $J = 8.41$, 1.97 Hz, 1H), 6.71 (s, 1H), 5.32 (s, 2H), 3.63 (m, 2H), 3.29 (br s, 1H), 3.09 (br s, 2H), 2.34 (t, $J = 4.57$ Hz, 2H), 2.20 (br s, 2H), 2.16 (s, 3H), 1.88 (d, $J = 8.86$ Hz, 3H), 1.80 (d, $J = 4.83$ Hz, 3H)
Ex. 335	^1H NMR (300 MHz, CDCl_3) δ 7.64 (app q, $J = 7.79$ Hz, 1H), 7.42 (t, $J = 7.65$ Hz, 1H), 7.33 (d, $J = 7.66$ Hz, 1H), 7.14 (d, $J = 7.65$ Hz, 1H), 7.00 (dt, $J = 8.76$, 2.21 Hz, 1H), 6.91 (dt, $J = 9.47$, 2.42 Hz, 1H), 6.17 (s, 1H), 5.29 (s, 2H), 3.98 - 3.92 (m, 1H), 3.80 - 3.77 (m, 3H), 3.59 (br s, 2H), 3.29 (t, $J = 4.43$ Hz, 2H), 2.04 (s, 3H), 2.00 (s, 3H)
Ex. 336	^1H NMR (300 MHz, CDCl_3) δ 7.65 (app q, $J = 7.79$ Hz, 1H), 7.43 - 7.32 (m, 2H), 7.12 (dd, $J = 7.66$, 1.21 Hz, 1H), 7.00 (dt, $J = 9.06$, 1.51 Hz, 1H), 6.92 (dt, $J = 9.42$, 2.52 Hz, 1H), 6.16 (s, 1H), 5.30 (s, 2H), 3.69 (t, $J = 5.04$ Hz, 2H), 3.39 (s, 3H), 3.26 (s, 1H), 3.19 (s, 1H), 2.91 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H)
Ex. 337	^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.91 (br s, 1H), 7.73 (app q, $J = 7.85$ Hz, 1H), 7.53 - 7.20 (m, 5H), 6.74 (s, 1H), 5.37 (s, 2H), 1.99 (s, 3H), 1.92 (s, 3H)

Example 338



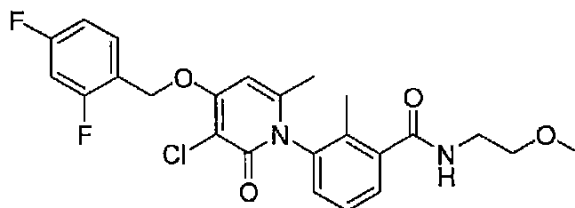
5

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[3-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

3-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 4 above) (2.0 g, 4.31

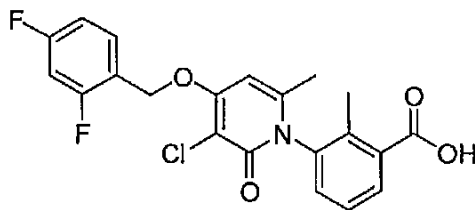
mmol) was cooled to 0°C in 10 ml of tetrahydrofuran. 19.5 ml of 1M BH₃·THF in tetrahydrofuran was added and stirred overnight, allowing the temperature to rise to room temperature. The reaction was cooled back down to 0°C and ice chips were added to quench the reaction. The slurry was extracted 3 times with an ethyl acetate/tetrahydrofuran mixture. The combined organic layers were washed with brine, dried over MgSO₄, filtered and evaporated to give a white solid (1.73 g, 89%). ¹H NMR (400 MHz, DMSO-d₆) δ 7.67 (app q, J = 7.92 Hz, 1H), 7.46 (d, J = 7.52 Hz, 1H), 7.32 (dt, J = 10.74, 2.42 Hz, 1H), 7.30 (t, J = 7.72 Hz, 1H), 7.17 (dt, J = 8.46, 1.88 Hz, 1H), 7.03 (d, J = 7.38 Hz, 1H), 6.68 (s, 1H), 5.32 (s, 2H), 4.51 (s, 2H), 3.29 (d, J = 9.40 Hz, 1H), 1.85 (s, 3H), 1.81 (s, 3H), LC/MS, t_r = 2.64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 450 (M+H). ES-HRMS m/z 450.0480 (M+H calcd for C₂₁H₁₈BrF₂NO₃ requires 450.0511).

Example 339



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-methoxyethyl)-2-methylbenzamide

Step 1: Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid.



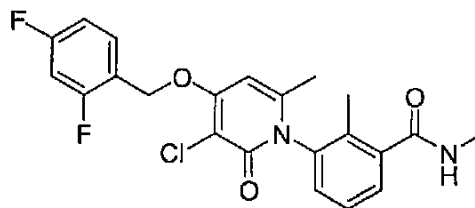
3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 3 above) (10.0 g, 25.9 mmol) was refluxed with *N*-chlorosuccinimide (4.15 g, 31.1 mmol) and dichloroacetic acid (1.06 ml, 12.9 mmol) in 50 ml of CH₂Cl₂ overnight. The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in acetonitrile for 30 minutes, washed 4 times with acetonitrile and dried *in vacuo* to yield a white solid (8.3 g, 78%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.93 (dd, *J* = 7.15, 1.92 Hz, 1H), 7.72 (app q, *J* = 7.92 Hz, 1H), 7.52 – 7.35 (m, 3H), 7.22 (dt, *J* = 8.47, 2.01 Hz, 1H), 6.80 (s, 1H), 5.38 (s, 2H), 2.14 (s, 3H), 1.93 (s, 3H); LC/MS, *t*_r = 2.64 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 420 (M+H). ES-HRMS *m/z* 420.0806 (M+H calcd for C₂₁H₁₆ClF₂NO₄ requires 420.0809).

Step 5: Preparation of the title compound. 3-[3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (from Step 1 above) (500 mg, 1.19 mmol) was dissolved in 5 ml of CH₂Cl₂. 2-Methoxyethylamine (129 μl, 1.49 mmol) was added, followed, in order, by EDCI (286 mg, 1.49 mmol), 1-hydroxybenzotriazole (202 mg, 1.49 mmol) and triethylamine (332 μl, 2.38 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH₄Cl and extracted 3 times with ethyl acetate. The combined organic layer was dried over MgSO₄ and evaporated. The resulting solid was dried *in vacuo* to give a white solid (401 mg, 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.56 (app q, *J* = 7.74 Hz,

1H), 7.47 (d, $J = 6.98$ Hz, 1H), 7.34 (t, $J = 7.72$ Hz, 1H),
7.11 (d, $J = 7.25$ Hz, 1H), 6.95 (dt, $J = 8.23, 1.66$ Hz, 1H),
6.87 (dt, $J = 9.51, 2.46$ Hz, 1H), 6.35 (br s, 1H), 6.15 (s,
1H), 5.25 (s, 2H), 3.72 - 3.63 (m, 1H), 3.58 - 3.49 (m, 3H),
5 3.35 (s, 3H), 2.09 (s, 3H), 1.93 (s, 3H); LC/MS, $t_r = 2.56$
minutes (5 to 95% acetonitrile/water over 5 minutes at 1
ml/min, at 254 nm, at 50°C), ES-MS m/z 477 (M+H). ES-HRMS m/z
477.1363 (M+H calcd for $C_{24}H_{23}ClF_2N_2O_4$ requires 477.1387).

10

Example 340

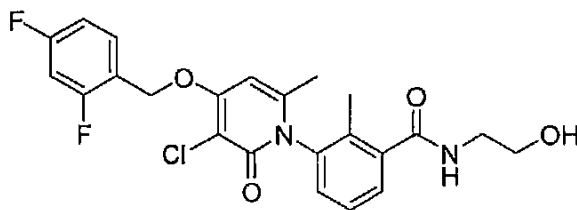


15

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-
1(2H)-yl]-N,2-dimethylbenzamide

The title compound was prepared by a procedure similar to the
20 one described for Example 337, where methylamine was used as
the amine and the product was obtained in 73% yield. 1H NMR
(300 MHz, DMSO- d_6) δ 8.37 (app d, $J = 4.64$ Hz, 1H), 7.72 (app
q, $J = 7.92$ Hz, 1H), 7.44 - 7.35 (m, 4H), 7.22 (dt, $J = 8.54,$
1.61 Hz, 1H), 6.78 (s, 1H), 5.37 (s, 2H), 2.79 (d, $J = 4.43$
25 Hz, 3H), 1.95 (s, 3H), 1.94 (s, 3H); LC/MS, $t_r = 2.46$ minutes
(5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at
254 nm, at 50°C), ES-MS m/z 433 (M+H). ES-HRMS m/z 433.1163
(M+H calcd for $C_{22}H_{19}ClF_2N_2O_3$ requires 433.1125).

Example 341



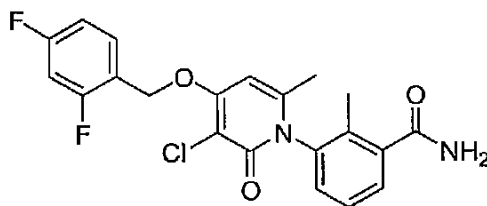
5

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-2-methylbenzamide

The title compound was prepared by a procedure similar to the one described for , where ethanolamine was used as the amine and the product was obtained in 65% yield. ¹H NMR (400 MHz, DMSO-d₆) δ 8.39 (t, *J* = 5.51 Hz, 1H), 7.67 (*app* q, *J* = 7.88 Hz, 1H), 7.43 - 7.33 (m, 3H), 7.23 (d, *J* = 7.25 Hz, 1H), 7.17 (dt, *J* = 8.39, 1.66 Hz, 1H), 6.74 (s, 1H), 5.32 (s, 2H), 3.48 (br s, 2H), 3.31 - 3.26 (m, 2H), 1.90 (s, 3H), 1.89 (s, 3H); LC/MS, *t_r* = 2.34 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS *m/z* 463 (M+H). ES-HRMS *m/z* 463.1220 (M+H calcd for C₂₃H₂₁ClF₂N₂O₄ requires 463.1231).

20

Example 342

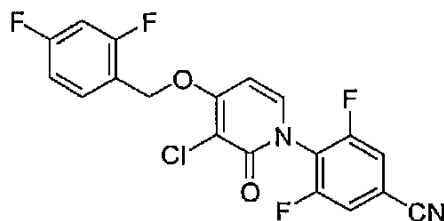


25

3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzamide

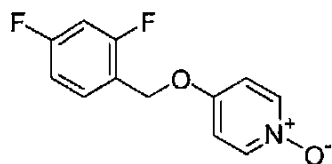
3-[3-Chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-2-methylbenzoic acid (Step 1 above) (500 mg, 1.19 mmol) was stirred with 2-chloro-4,6-dimethoxy-1,3,5-triazine (251 mg, 1.43 mmol) and *N*-methylmorpholine (392 μ l, 3.57 mmol) in 5 ml of tetrahydrofuran at room temperature for 2 hours. 2.5 ml of NH_4OH was added and stirred at room temperature for 2.5 hours. The reaction was diluted with tetrahydrofuran and ethyl acetate and extracted. The combined organic layers were washed with NaHCO_3 , 1 N HCl, and brine, dried over MgSO_4 , filtered and evaporated. The resulting solid was dried *in vacuo* to obtain a white solid (313 mg, 63%). ^1H NMR (400 MHz, DMSO- d_6) δ 7.87 (br s, 1H), 7.66 (q, J = 7.83 Hz, 1H), 7.48 - 7.30 (m, 3H), 7.23 (d, J = 7.52 Hz, 1H), 7.17 (t, J = 7.65 Hz, 1H), 6.73 (s, 1H), 5.32 (s, 2H), 1.94 (s, 3H), 1.88 (s, 3H); LC/MS, t_r = 2.44 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min, at 254 nm, at 50°C), ES-MS m/z 419 ($\text{M}+\text{H}$). ES-HRMS m/z 419.0963 ($\text{M}+\text{H}$ calcd for $\text{C}_{21}\text{H}_{17}\text{ClF}_2\text{N}_2\text{O}_3$ requires 419.0969).

Example 343



4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]pyridine 1-oxide .

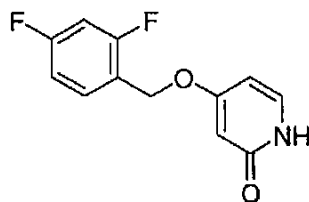


5

2, 4-difluorobenzyl alcohol (100. g, 0.694 mol) and 4-nitropyridine N-oxide (98. g, 0.700 mol) are combined with 250 g Cs_2CO_3 (1.1 eq) in 2.5 L anhydrous dimethylformamide and heated to 80°C with stirring. The reaction was followed by ^{19}F -NMR (crude reaction mixture with external D_2O reference) and complete after 40 h. The mixture was filtered hot; product crystallized out on cooling. 90.21 g (55%) of white plates were collected by filtration and washed with diethyl ether. The mother liquor was diluted with 2.5 L diethyl ether and stored in the freezer overnight, yielding a second crop 68.76 g (41%, combined yield 96%). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.06 (m, 2 H), 7.61 (quartet, $J = 8.45$ Hz, 1H), 7.30 (t, $J = 10.37$ Hz, 1H), 7.12, (t, $J = 8.45$ Hz, 1H), 7.09 (d, $J = 5.06$ Hz, 2H), 5.14 (s, 2H). ^{19}F -NMR (400 MHz, $\text{DMSO}-d_6$) δ -109.43 (quintet, $J = 7.78$ Hz, 1F), -113.82 (quartet, $J = 9.55$ Hz, 1F). LC/MS $t_r = 3.90$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 238 ($\text{M}+\text{H}$).

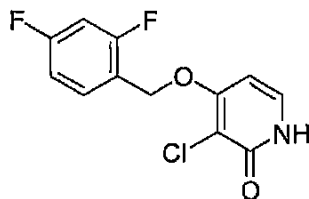
25

Step 2: Preparation of 4-[(2,4-difluorobenzyl)oxy]-pyridin-2(1H)-one (7).



4-[(2,4-difluorobenzyl)oxy]pyridine 1-oxide (from Step 1)
(30.0 g , 0.127 mol), anhydrous potassium acetate (25 g, 0.25
5 mol), acetic anhydride (25 g, 0.25 mol), and 10 ml acetic acid
were combined in a 250-ml round-bottomed flask with overhead
stirring and heated to 130°C for 4 hours. The mixture was
concentrated under vacuum, the solids dissolved in 95 ml
acetonitrile: 5 ml water, filtered through charcoal and poured
10 into 600 ml ice with stirring. The mixture was allowed to
stand overnight at room temperature, then 9.62 g (30%) product
collected by filtration as a medium brown solid (adequate for
the next step without purification). ¹H-NMR (400 MHz, DMSO-*d*₆)
δ 11.10 (s, 1H), 7.59 (quartet, *J* = 9.91 Hz, 1H), 7.29 (t, *J* =
15 10.36 Hz, 1H), 7.21 (d, *J* = 8.20 Hz, 1H), 7.11 (t, *J* = 8.48
Hz, 1H), 5.83 (m, 2H), 5.02 (s, 2H). ¹⁹F-NMR (400 MHz, DMSO-
*d*₆) δ -109.57 (quintet, *J* = 7.66 Hz, 1F) -113.88 (quartet, *J* =
8.93 Hz, 1F). LC/MS *t*_r = 4.29 minutes (0-95%
acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes
20 at 1 ml/min with detection at 254 nm, at 50°C) ES-MS *m/z* 238
(M+H).

Step 3: Preparation of 3-chloro-4-[(2,4-
difluorobenzyl)oxy]pyridin-2(1H)-one .



4-[(2,4-difluorobenzyl)oxy]-pyridin-2(1H)-one (from Step 2)
(8.60 g, 36.3 mmol) was stirred in 150 ml dimethylformamide
and treated with N-chlorosuccinimide (5.4 g, 39.9 mmol).

After 15 hours, the precipitate was collected by filtration

5 (5.11 g, 52%) yeilding a lustrous white solid. The mother
liquor was diluted to 500 ml with diethyl ether, providing
2.47 g (25%) in a second crop. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ
11.87 (s, 1H), 7.60 (quartet, $J = 6.34$ Hz, 1H), 7.43 (d, $J =$
7.58 Hz, 1H), 7.31 (dt, $J = 10.08, 2.21$ Hz, 1H), 7.14 (dt, $J =$
10 8.65, 1.79 Hz, 1H), 6.44 (d, $J = 7.49$ Hz, 1H), 5.28 (s, 1H).

$^{19}\text{F-NMR}$ (400 MHz, DMSO-d_6) δ -109.58 (quintet, $J = 7.75$ Hz, 1F),
-113.68 (quartet, $J = 8.68$ Hz, 1F). LC/MS $t_r = 4.47$ minutes
(0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6
minutes at 1 ml/min with detection at 254 nm, at 50°C) ES-MS
15 m/z 272, 274 3:1 (M+H).

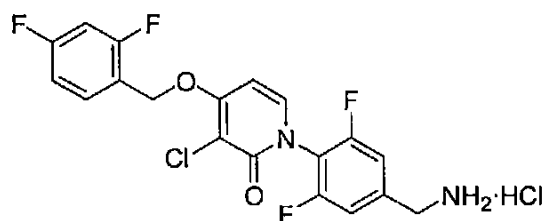
Step 4: Preparation of the title compound .

3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (from
step 3) (3.25 g, 11.9 mmol) was combined with Cs_2CO_3 (3.93 g,
20 12.1 mmol) in 50 ml dimethylformamide and heated to 70°C,
stirring under nitrogen. 3,4,5-trifluorobenzonitrile (1.83 g,
11.9 mmol) was added. After 4 hours, the mixture was
filtered, concentrated in vacuo, washed thrice with hot
cyclohexane, dissolved in tetrahydrofuran, treated with MgSO_4
25 and charcoal, and filtered. The solution was evaporated
leaving a fine white solid (3.99 g, 82%). $^1\text{H-NMR}$ (400 MHz,
 DMSO-d_6) δ 8.12 (d, $J = 7.59$ Hz, 2H), 7.92 (d, $J = 8.31$ Hz,
1H), 7.65 (quartet, $J = 6.77$, 1H), 7.34 (dt, $J = 9.81, 2.71$
Hz, 1H), 7.16 (dt, $J = 8.59, 2.50$ Hz, 1H), 6.87 (d, $J = 8.01$
30 Hz, 1H), 5.39 (s, 2H). $^{19}\text{F-NMR}$ (400 MHz, DMSO-d_6) δ -109.17
(quintet, $J = 8.97$ Hz, 1F), -113.51 (quartet, $J = 9.53$ Hz,
1F), -116.32 (d, $J = 7.69$ Hz, 2F). LC/MS $t_r = 5.51$ minutes (0-

95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 409 ($M+H$). ES-HRMS m/z 409.0351 ($M+H$ calcd for $C_{19}H_{10}ClF_4N_2O_2$ requires 409.0361).

5

Example 344

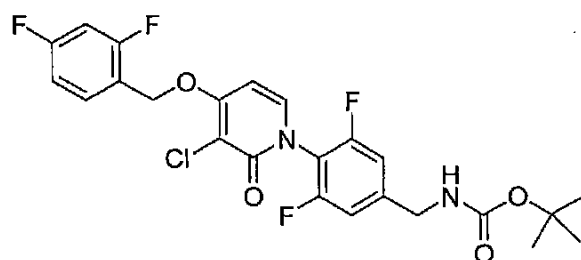


10

1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride

Step 1: Preparation of tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate .

15



20

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (2.84 g, 6.95 mmol), di-*t*-butyl-dicarbonate (3.18 g, 14.6 mmol), and nickel(II) chloride (0.90 g, 6.95 mmol) were combined with 40 ml methanol and 40 ml tetrahydrofuran and cooled to 0°C stirring in an ice bath.

25

Sodium borohydride (1.33 g, 35.2 mmol) was added in small

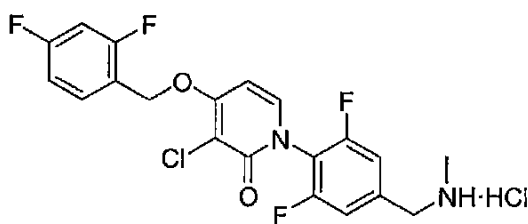
portions over 10 minutes to control foaming, and the reaction was stirred 1 hour. Additional sodium borohydride (0.50 g, 13.2 mmol) was required to force the reaction to completion by LC. A color change from yellow to black persisted on completion. The mixture was filtered through a bed of charcoal layered on anhydrous MgSO_4 and evaporated to dryness. Excess di-*t*-butyl-dicarbonate and byproduct *t*-butanol were removed by repeated heating with water to 80°C in *vacuo*, giving the product as a fine white powder (3.11 g, 87%). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.89 (d, J = 8.04 Hz, 1H), 7.65 (quartet, J = 6.73 Hz, 1H), 7.55 (t, J = 6.73 Hz, 1H), 7.34, (dt, J = 10.05, 2.51 Hz, 1H), 7.16 (m, 3H), 6.77 (d, J = 8.18 Hz, 1H), 5.34 (s, 2H), 4.18 (d, J = 5.68 Hz, 2H), 1.34 (s, 9H). ^{19}F -NMR (400 MHz, $\text{DMSO}-d_6$) δ -109.26 (quintet, J = 6.91 Hz, 1F), -113.53 (quartet, J = 7.73 Hz, 1F), -120.32 (d, J = 8.91 Hz, 2F). LC/MS t_r = 5.90 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 513 (M+H). ES-HRMS m/z 513.1164 (M+H calcd for $\text{C}_{24}\text{H}_{22}\text{ClF}_4\text{N}_2\text{O}_4$ requires 513.1199).

Step 2: Preparation of the title compound .

tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate (from step 3) (1.39 g, 2.71 mmol) was dissolved in 20 ml tetrahydrofuran and treated with 4 ml concentrated hydrochloric acid. The solution was evaporated and dried in *vacuo* to a fine white solid (1.20 g, 99%). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.54 (m, 2H), 7.86 (d, J = 7.57 Hz, 1H), 7.65 (quartet, J = 7.62, 1H), 7.50 (d, J = 9.25 Hz, 2H), 7.34 (dt, J = 10.50, 2.45 Hz, 1H), 7.16 (dt, J = 8.38, 2.55 Hz, 1H), 6.78 (d, J = 7.86 Hz, 1H), 5.37 (s, 2H), 4.10 (br s, 2H), 4.97-3.14 (v br s, 3H). ^{19}F -NMR

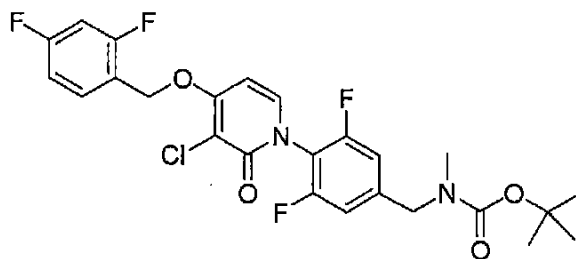
(400 MHz, DMSO- d_6) δ -109.21 (quintet, J = 7.77 Hz, 1F), -113.51 (quartet, J = 8.95 Hz, 1F), -119.56 (d, J = 9.44 Hz, 2F). LC/MS t_r = 4.33 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 413 (M+H). ES-HRMS m/z 413.0712 (M+H calcd for $C_{19}H_{14}ClF_4N_2O_2$ requires 413.0674).

Example 345



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-{2,6-difluoro-4-[(methylamino)methyl]phenyl}pyridin-2(1H)-one hydrochloride

Step 1: Preparation of tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(methyl)carbamate .



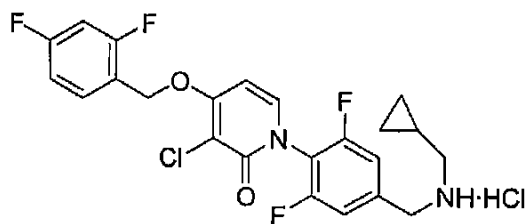
tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzylcarbamate (from Step 1) (252 mg, 0.491 mmol) and iodomethane (75 mg, 0.528 mmol) are combined in 8 ml anhydrous dimethylformamide. Sodium hydride 60% in mineral oil (30 mg, 0.75 mmol) was added and

the mixture stirred under nitrogen at room temperature for 1 hour. Saturated aqueous NH_4Cl was added (4 ml) followed by 20 ml water and the product was extracted into ethyl acetate, washed with brine, dried over MgSO_4 , filtered, and evaporated to give the product as a white powder (208 mg, 80%). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.87 (d, $J = 7.85$ Hz, 1H), 7.64 (quartet, $J = 6.66$ Hz, 1H), 7.32, (dt, $J = 9.39, 3.29$ Hz, 1H), 7.13 (m, 3H), 6.77 (d, $J = 7.94$ Hz, 1), 5.38 (s, 2H), 4.43 (s, 2H), 2.90 (s, 3H), 1.40 (br m, 9H). ^{19}F -NMR (400 MHz, $\text{DMSO}-d_6$) δ -109.25 (quintet, $J = 8.93$ Hz, 1F), -113.53 (quartet, $J = 9.73$ Hz, 1F), -119.89 (d, $J = 9.35$ Hz, 2F). LC/MS $t_r = 6.16$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 527 (M+H). ES-HRMS m/z 527.1338 (M+H calcd for $\text{C}_{25}\text{H}_{24}\text{ClF}_4\text{N}_2\text{O}_4$ requires 527.1355).

Step 2: Preparation of the title compound .

tert-butyl 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl(methyl)carbamate (from step 1) (188 mg, 0.357 mmol) was subjected to the conditions of Step 2, yielding a fine white solid (165 mg, 100%). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.30 (br s, 2H), 7.89 (d, $J = 7.99$ Hz, 1H), 7.65 (quartet, $J = 7.64$, 1H), 7.55 (d, $J = 8.66$ Hz, 2H), 7.34 (dt, $J = 9.93, 2.57$ Hz, 1H), 7.17 (dt, $J = 8.49, 2.48$ Hz, 1H), 6.81 (d, $J = 8.01$ Hz, 1H), 5.39 (s, 2H), 4.21 (s, 2H), 2.56 (s, 3H). ^{19}F -NMR (400 MHz, $\text{DMSO}-d_6$) δ -109.20 (quintet, $J = 7.56$ Hz, 1F), -113.52 (quartet, $J = 9.67$ Hz, 1F), -119.21 (d, $J = 8.79$ Hz, 2F). LC/MS $t_r = 4.30$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 427 (M+H). ES-HRMS m/z 427.0816 (M+H calcd for $\text{C}_{20}\text{H}_{16}\text{ClF}_4\text{N}_2\text{O}_2$ requires 427.0831).

Example 346



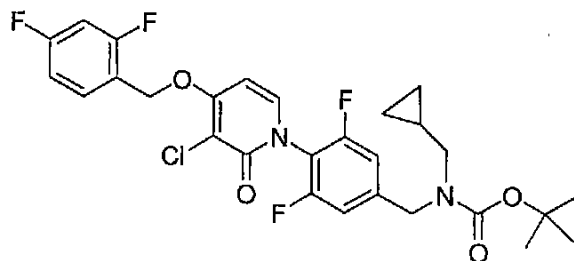
5

3-chloro-1-((4-((cyclopropylmethyl)amino)methyl)-2,6-difluorophenyl)-4-((2,4-difluorobenzyl)oxy)pyridin-2(1H)-one hydrochloride

10 The title compound was prepared by direct analogy with , replacing iodomethane with bromocyclopropylmethane and extending the reaction time to 6 hours in Step 1.

Step 1:

15



1 tert-butyl 4-[3-chloro-4-((2,4-difluorobenzyl)oxy)-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl (cyclopropylmethyl) carbamate

20

¹H-NMR (400 MHz, DMSO-d₆) δ 7.89 (d, *J* = 7.91 Hz, 1H), 7.65 (quartet, *J* = 6.81 Hz, 1H), 7.33, (dt, *J* = 9.90, 2.26 Hz, 1H), 7.17 (m, 3H), 6.77 (d, *J* = 7.90 Hz, 1), 5.38 (s, 2H), 4.51 (s, 2H), 3.10 (br s, 2H), 1.36 (m, 9H), 0.97 (br s, 1H), 0.38 (m, 25 2H), 0.18 (m, 2H). ¹⁹F-NMR (400 MHz, DMSO-d₆) δ -109.25

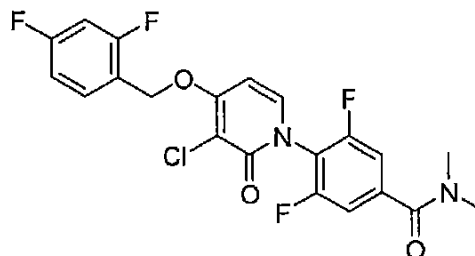
(quintet, $J = 7.77$ Hz, 1F), -113.54 (quartet, $J = 9.02$ Hz, 1F), -120.24 (m, 2F). LC/MS $t_r = 5.99$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 567 (M+H). ES-HRMS m/z 567.1653 (M+H calcd for $C_{28}H_{28}ClF_4N_2O_4$ requires 567.1668).

Step 2: Title compound .

1H -NMR (400 MHz, DMSO- d_6) δ 9.51 (br s, 2H), 7.87 (d, $J = 7.96$ Hz, 1H), 7.63 (m, 3H), 7.33 (dt, $J = 9.93$, 2.65 Hz, 1H), 7.16 (dt, $J = 8.36$, 2.32 Hz, 1H), 6.81 (d, $J = 7.92$ Hz, 1H), 5.38 (s, 2H), 4.22 (br s, 2H), 2.82 (br s, 2H), 1.10 (m, 1H), 0.57 (m, 2H), 0.36 (m, 2H). ^{19}F -NMR (400 MHz, DMSO- d_6) δ -109.25 (quintet, $J = 7.69$ Hz, 1F), -113.54 (quartet, $J = 9.35$ Hz, 1F), -120.24 (m, 2F). LC/MS $t_r = 4.55$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 467 (M+H). ES-HRMS m/z 467.1119 (M+H calcd for $C_{23}H_{20}ClF_4N_2O_2$ requires 467.1144).

20

Example 347

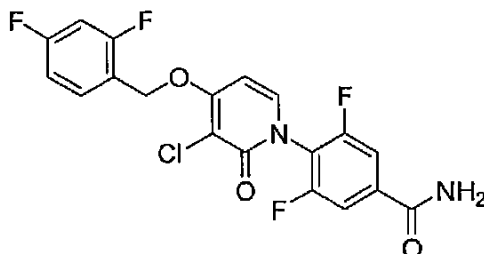


25

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluoro-N,N-dimethylbenzamide

Step 1: Preparation of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzamide.

5



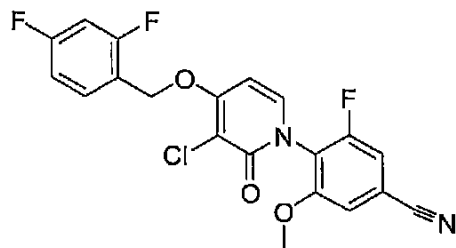
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (540 mg, 1.32 mmol) and
 10 potassium trimethylsilanolate 90% (375 mg, 2.63 mmol) are combined in 8 ml anhydrous toluene and heated to reflux with stirring. After 10 minutes, the mixture allowed to cool then partitioned between saturated aqueous ammonium chloride and ethyl acetate. The aqueous layer is extracted twice with
 15 ethyl acetate, the combined organics are washed with brine, dried over MgSO_4 , and evaporated *in vacuo*. The crude product is taken up in tetrahydrofuran and filtered through charcoal layered over silica gel, and the solution evaporated *in vacuo* to give the product as a white powder (468 mg, 83%). $^1\text{H-NMR}$
 20 (400 MHz, $\text{DMSO}-d_6$) δ 8.22 (br s, 2H), 7.92 (d, $J = 7.84$ Hz, 1H), 7.78 (d, $J = 8.45$, 2H), 7.65 (quartet, $J = 8.40$ Hz, 1H), 7.34, (dt, $J = 10.09$, 2.58 Hz, 1H), 7.17 (dt, $J = 8.72$, 2.30 Hz, 1H), 6.83 (d, $J = 7.91$ Hz, 1H), 5.39 (s, 2H). $^{19}\text{F-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ -109.21 (quintet, $J = 7.43$ Hz, 1F), -113.52
 25 (quartet, $J = 9.62$ Hz, 1F), -118.74 (d, $J = 8.88$ Hz, 2F). LC/MS $t_r = 4.67$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS m/z 427 (M+H). ES-HRMS m/z 427.0454 (M+H calcd for $C_{19}H_{12}ClF_4N_2O_3$ requires 427.0467).

Step 2: Preparation of the title compound .

5 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzamide (from step 1) (243 mg, 0.357 mmol) was subjected to the conditions of Step 1, with the exception that two equivalents of sodium hydride 60% in mineral oil and iodomethane were used instead of one (46 mg, 0.69 mmol and 103
10 mg, 0.724 mmol respectively). 1H -NMR (400 MHz, DMSO- d_6) δ 7.92 (d, J = 7.76 Hz, 1H), 7.66 (quartet, J = 7.33, 1H), 7.44 (d, J = 7.59 Hz, 2H), 7.34 (dt, J = 9.88, 2.63 Hz, 1H), 7.17 (dt, J = 8.35, 2.06 Hz, 1H), 6.83 (d, J = 7.55 Hz, 1H), 5.39 (s, 2H), 2.98 (s, 3H), 2.91 (s, 3H). ^{19}F -NMR (400 MHz, DMSO-
15 d_6) δ -109.22 (quintet, J = 8.10 Hz, 1F), -113.53 (quartet, J = 9.18 Hz, 1F), -118.88 (d, J = 7.77 Hz, 2F). LC/MS t_r = 5.13 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 455 (M+H). ES-HRMS m/z 455.0791 (M+H calcd for
20 $C_{21}H_{16}ClF_4N_2O_3$ requires 455.0780).

Example 348

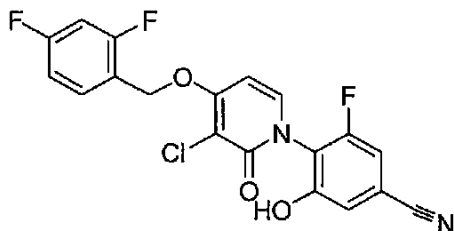


25

4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-methoxybenzonitrile

Step 1: Preparation of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-hydroxybenzonitrile .

5



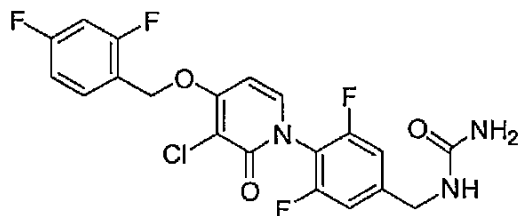
4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (522 mg, 1.28 mmol) and
 10 potassium trimethylsilonate 90% (655 mg, 4.60 mmol) are combined in 8 ml anhydrous tetrahydrofuran and stirred under nitrogen at room temperature for 2 hours. The precipitated potassium salt of was collected by filtration, washed with a minimum of tetrahydrofuran, and dried *in vacuo*. A portion of
 15 this salt (275 mg, 0.618 mmol) was dissolved in 5 ml water, the pH was adjusted below 6 with concentrated hydrochloric acid, the product collected by filtration, washed with water, sucked dry under a blanket of dry nitrogen, and dried further *in vacuo* overnight (251 mg, 100%, 98% overall). ¹H-NMR (400
 20 MHz, DMSO-*d*₆) δ 11.46 (br s, 1H), 7.74 (d, *J* = 7.81 Hz, 1H), 7.67 (quartet, *J* = 6.76 Hz, 1H), 7.52 (d, *J* = 8.76, 1H), 7.364, (dt, *J* = 10.18, 2.37 Hz, 1H), 7.24 (br s, 1H), 7.17 (br t, *J* = 8.75, 1H), 6.74 (d, *J* = 8.04 Hz, 1H), 5.39 (s, 2H). ¹⁹F-NMR (400 MHz, DMSO-*d*₆) δ -109.26 (quintet, *J* = 8.50 Hz, 1F),
 25 -113.52 (quartet, *J* = 9.29 Hz, 1F), -118.06 (d, *J* = 9.38 Hz, 1F). LC/MS *t*_r = 5.13 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes, then 95% acetonitrile for 2 minutes, at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS m/z 407 ($M+H$). ES-HRMS m/z 407.0381 ($M+H$ calcd for $C_{19}H_{11}ClF_3N_2O_3$ requires 407.0405).

Step 2: Preparation of the title compound .

5 The potassium salt of 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3-fluoro-5-hydroxybenzonitrile (from Step 1) (273 mg, 0.614 mmol) was stirred in 5 ml anhydrous dimethylformamide under nitrogen. Iodomethane (93 mg, 0.66 mmol) was added, and stirring continued for 2 hr. The mixture
10 was diluted to 50 ml with ice-cold water, and the white precipitate collected by filtration. The precipitate was washed thrice with water, sucked dry under a blanket of nitrogen, and dried further in vacuo overnight (242 mg, 87%).
 1H -NMR (400 MHz, DMSO- d_6) δ 7.73 (m, 2H), 7.65 (m, 2H), 7.34 (dt, J = 9.90, 2.39 Hz, 1H), 7.17 (dt, J = 8.75, 2.47 Hz, 1H),
15 6.75 (d, J = 7.97 Hz, 1H), 5.37 (s, 2H), 3.84 (s, 3H). ^{19}F -NMR (400 MHz, DMSO- d_6) δ -109.24 (quintet, J = 7.85 Hz, 1F), -113.54 (quartet, J = 9.83 Hz, 1F), -118.33 (d, J = 7.77 Hz, 1F). LC/MS t_r = 5.40 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with
20 detection at 215 nm, at 50°C) ES-MS m/z 421 ($M+H$). ES-HRMS m/z 421.0522 ($M+H$ calcd for $C_{20}H_{13}ClF_3N_2O_3$ requires 421.0561).

25 Example 349

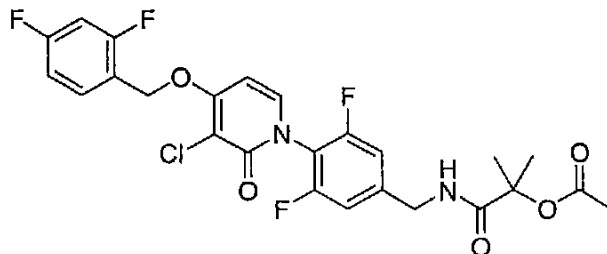


N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}urea

Step 1: Preparation of the title compound

5 1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (162 mg, 0.361 mmol) is dissolved in 4 ml 50% aqueous acetic acid and treated with potassium cyanate (59 mg, 0.72 mmol). The mixture was stirred 2 hr, then the mixture was diluted to 50
10 ml with cold water, and the crude product, contaminated with the acetamide, was purified by silica gel chromatography, eluting first with 20% ethanol in hexane then 40% ethanol in hexane. The 50% fractions were pooled by TLC and evaporated, giving the product as a fine white powder (65 mg, 40%). ¹H-NMR
15 (400 MHz, DMSO-*d*₆) δ 7.87 (d, *J* = 8.07 Hz, 1H), 7.64 (quartet, *J* = 6.53 Hz, 1H), 7.33, (dt, *J* = 9.47, 1.99 Hz, 1H), 7.15 (m, 3H), 6.76 (d, *J* = 7.97 Hz, 1H), 6.59 (m, 1H), 5.65 (br s, 2H), 5.38 (s, 2H), 4.22 (m, 2H). ¹⁹F-NMR (400 MHz, DMSO-*d*₆) δ -
109.22 (quintet, *J* = 7.86 Hz, 1F), -113.51 (quartet, *J* = 9.40
20 1F), -120.65 (d, *J* = 8.75 Hz, 2). LC/MS *t*_r = 4.85 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 456 (M+H).

25 Example 350

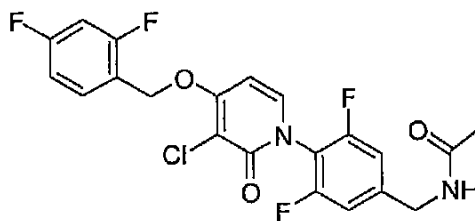


2-({4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}amino)-1,1-dimethyl-2-oxoethyl acetate

5 Step 1: Preparation of the title compound
1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (225 mg, 0.501 mmol) is dissolved in a solution of 10 ml tetrahydrofuran and triethylamine (111 mg, 1.10 mmol). 2-acetoxy-2-methyl-propionyl chloride (85 mg, 0.516 mmol) is
10 added, and the mixture stirred for 30 minutes before partitioning between saturated aqueous ammonium chloride and ethyl acetate. The layers are separated, and the aqueous phase extracted twice with ethyl acetate. The combined
15 organics are washed with water and brine, then dried over MgSO_4 , filtered, and evaporated in vacuo, giving the product as a fine white powder (254 mg, 94%). $^1\text{H-NMR}$ (400 MHz, DMSO-d_6) δ 8.47 (t, $J = 6.16$ Hz, 1H), 7.88 (d, $J = 7.71$ Hz, 1H), 7.65 (quartet, $J = 7.24$ Hz, 1H), 7.34, (dt, $J = 10.04$, 2.49
20 Hz, 1H), 7.16 (m, 3H), 6.77 (d, $J = 7.78$ Hz, 1H), 5.38 (s, 2H), 4.32 (d, $J = 5.93$ 2H), 2.02 (s, 3H), 1.48 (s, 6H). $^{19}\text{F-NMR}$ (400 MHz, DMSO-d_6) δ -109.26 (quintet, $J = 9.00$ Hz, 1F), -113.52 (quartet, $J = 9.52$ Hz, 1F), -120.62 (d, $J = 9.09$ Hz, 2F). LC/MS $t_r = 5.43$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with
25 detection at 215 nm, at 50°C) ES-MS m/z 541 (M+H). ES-HRMS m/z 541.1128 (M+H calcd for $\text{C}_{25}\text{H}_{22}\text{ClF}_4\text{N}_2\text{O}_5$ requires 541.1148).

Example 351

30

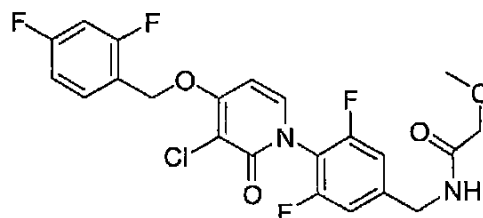


N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}acetamide

5

The compound was prepared in the following the produre for Example 350, substituting acetyl chloride (24 mg, 0.30 mmol) for 2-acetoxy-2-methyl-propionyl chloride. (128 mg, 96%). ¹H-NMR (400 MHz, DMSO-d₆) δ 8.48 (br s, 1H), 7.87 (d, J = 7.28 Hz, 1H), 7.64 (quartet, J = 8.01 Hz, 1H), 7.33, (dt, J = 9.87, 2.25 Hz, 1H), 7.17 (m, 3H), 6.76 (d, J = 8.25 Hz, 1H), 5.38 (s, 2H), 4.30 (m, 2H), 1.88 (s, 3H). ¹⁹F-NMR (400 MHz, DMSO-d₆) δ -109.22 (quintet, J = 8.04 Hz, 1F), -113.52 (quartet, J = 9.91 Hz, 1F), -120.43 (d, J = 8.77 Hz, 2F). LC/MS t_r = 5.04 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 555 (M+H). ES-HRMS m/z 455.0824 (M+H calcd for C₂₁H₁₆ClF₄N₂O₃ requires 455.0780).

20 Example 352

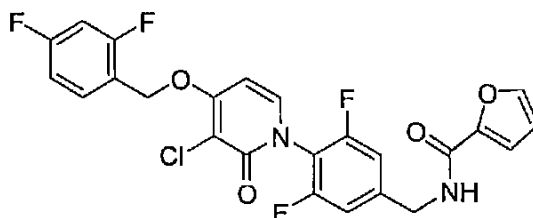


N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-methoxyacetamide

25

The compound was prepared in the following the produre for
 EXAMPLE 350, substituting 2-methoxy-acetyl chloride (45 mg,
 0.415 mmol) for 2-acetoxy-2-methyl-propionyl chloride. (124
 mg, 78%). ¹H-NMR (400 MHz, DMSO-d₆) δ 8.56 (t, *J* = 6.77 Hz,
 1H), 7.90 (d, *J* = 7.85 Hz, 1H), 7.67 (quartet, *J* = 7.67 Hz,
 1H), 7.36, (dt, *J* = 10.03, 2.36 Hz, 1H), 7.20 (m, 3H), 6.79
 (d, *J* = 8.07 Hz, 1H), 5.40 (s, 2H), 4.37 (d, *J* = 6.28 Hz,
 2H), 3.91(s, 2H), 3.35 (s, 3 H). ¹⁹F-NMR (400 MHz, DMSO-d₆) δ -
 109.23 (quintet, *J* = 8.29 Hz, 1F), -113.50 (quartet, *J* = 9.36
 Hz, 1F), -120.43 (d, *J* = 9.07 Hz, 2F). LC/MS t_r = 5.13
 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic
 acid, over 6 minutes at 1 ml/min with detection at 215 nm, at
 50°C) ES-MS *m/z* 485 (M+H). ES-HRMS *m/z* 485.0856 (M+H calcd
 for C₂₂H₁₈ClF₄N₂O₄ requires 485.0886).

Example 353



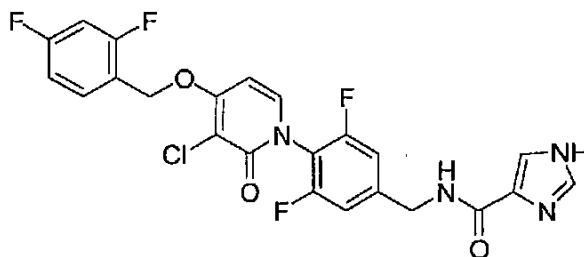
N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-
 yl]-3,5-difluorobenzyl}-2-furamide

The compound was prepared in the following the produre for
 EXAMPLE 350, substituting furoyl chloride (62 mg, 0.48 mmol)
 for 2-acetoxy-2-methyl-propionyl chloride. Yield: 142 mg, 85%.
¹H-NMR (400 MHz, DMSO-d₆) δ 9.07 (t, *J* = 6.14 Hz, 1H), 7.90 (d,
J = 7.88 Hz, 1H), 7.87 (dd, *J* = 1.69, 0.80 Hz, 1H), 7.67 (td,
J = 8.46, 6.80 Hz, 1H), 7.35, (dt, *J* = 10.00, 2.81 Hz, 1H),
 7.26 (d, *J* = 8.78 Hz, 2H), 7.18 (ddt, *J* = 8.58, 2.30, 1.07 Hz,

1H), 7.16 (dd, $J = 3.52, 0.77$ Hz, 1H), 6.79 (d, $J = 8.07$ Hz, 1H), 6.64 (dd, $J = 3.16, 1.73$ Hz, 1H), 5.40 (s, 2H), 4.49 (d, $J = 6.13$ Hz, 2H). ^{19}F -NMR (400 MHz, DMSO- d_6) δ -109.23 (quintet, $J = 7.65$ Hz, 1F), -113.50 (quartet, $J = 9.84$ Hz, 1F), -120.29 (d, $J = 9.41$ Hz, 2F). LC/MS $t_r = 5.32$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 507 (M+H). ES-HRMS m/z 507.0716 (M+H calcd for $\text{C}_{24}\text{H}_{16}\text{ClF}_4\text{N}_2\text{O}_4$ requires 507.0729).

10

Example 354



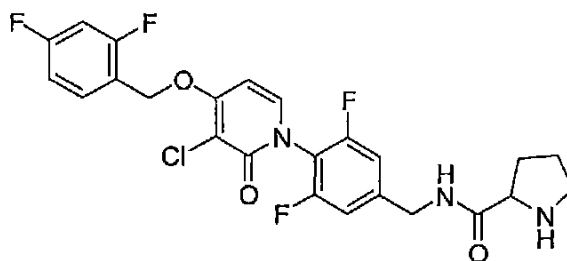
15 N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-1H-imidazole-4-carboxamide

Step 1: Preparation of the title compound

1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride (150 mg, 0.334 mmol) is dissolved in a solution of 4 ml tetrahydrofuran and triethylamine (35 mg, 0.35 mmol). 4-imidazolecarboxylic acid (62 mg, 0.56 mmol), 1-hydroxybenzotriazole hydrate (90 mg, 0.67 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (128 mg, 0.668 mmol), and triethylamine (100. mg, 0.989 mmol) were combined in 5 ml tetrahydrofuran and stirred under nitrogen. The solution containing 1-[4-(aminomethyl)-2,6-difluorophenyl]-3-chloro-4-

[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one hydrochloride was added in one portion, rinsing with 2 ml tetrahydrofuran. Stirring was continued at room temperature overnight, then the reaction was poured into 90 ml of icewater, and the product
 5 collected by filtration and dried *in vacuo* (254 mg, 94%). ¹H-NMR (400 MHz, DMSO-*d*₆) δ 12.55 (br s, 1H), 8.73 (t, *J* = 6.57 Hz, 1H), 7.90 (d, *J* = 7.87 Hz, 1H), 7.75 (s, 1H), 7.67 (m, 2H), 7.35, (dt, *J* = 10.04, 2.54 Hz, 1H), 7.21 (m, 3H), 6.78 (d, *J* = 8.04 Hz, 1H), 5.39 (s, 2H), 4.47 (m, 2H). ¹⁹F-NMR
 10 (400 MHz, DMSO-*d*₆) δ -109.26 (quintet, *J* = 7.87 Hz, 1F), -113.52 (quartet, *J* = 9.30 Hz, 1F), -120.59 (d, *J* = 9.21 Hz, 2F). LC/MS *t*_r = 4.48 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 507 (M+H). ES-HRMS
 15 *m/z* 507.0818 (M+H calcd for C₂₃H₁₆ClF₄N₄O₃ requires 507.0842).

Example 355



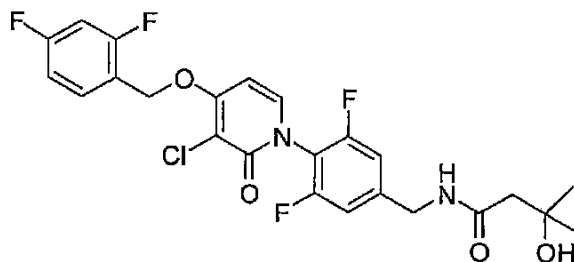
N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-5-oxoproline

25 Step 1: Preparation of the title compound

The compound was prepared following the procedure for Example 354, substituting 2-pyrrolidone-5-carboxylic acid for 4-imidazolecarboxylic acid. ¹H-NMR (400 MHz, DMSO-*d*₆) δ 8.67 (t,

$J = 6.08$ Hz, 1H), 7.88 (m, 1H), 7.65 (qr, $J = 7.57$, 1H), 7.34, (dt, $J = 9.32$, 2.63 Hz, 1H), 7.22 (d, $J = 9.36$, 2H), 7.17 (dt, $J = 8.51$, 2.55 Hz, 1H), 6.77 (d, $J = 7.66$ Hz, 1H), 5.73 (s, 1H), 5.38 (s, 2H), 4.35 (d, $J = 5.74$, 2H), 4.05 (m, 1H), 2.15
 5 (m, 2H), 1.90 (m, 2H). ^{19}F -NMR (400 MHz, DMSO- d_6) δ -109.25 (quintet, $J = 7.72$ Hz, 1F), -113.52 (quartet, $J = 8.94$ Hz, 1F), -120.39 (d, $J = 9.11$ Hz, 2F). LC/MS $t_r = 4.81$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS
 10 m/z 524 (M+H). ES-HRMS m/z 524.0998 (M+H calcd for $\text{C}_{24}\text{H}_{19}\text{ClF}_4\text{N}_3\text{O}_4$ requires 524.0995).

Example 356



N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-3-hydroxy-3-methylbutanamide

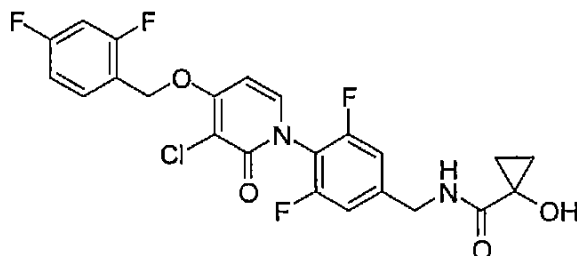
Step 1: Preparation of the title compound

The compound was prepared following the procedure for , substituting 2-hydroxy-2-methyl butyric acid for 4-

imidazolecarboxylic acid. ^1H -NMR (400 MHz, DMSO- d_6) δ 8.43 (t, $J = 6.04$ Hz, 1H), 7.88 (d, $J = 8.01$, 1H), 7.65 (qr, $J = 6.84$, 1H), 7.34, (dt, $J = 10.13$, 2.55 Hz, 1H), 7.22 (d, $J = 8.74$, 2H), 7.16 (dt, $J = 8.57$, 2.45 Hz, 1H), 6.77 (d, $J = 7.89$ Hz, 1H), 5.38 (s, 2H), 4.75 (s, 0.5H (OH)), 4.35 (d, $J = 6.48$,

2H), 2.28 (s, 2H), 1.47 (s, 0.5H(OH)), 1.16 (s, 6H). ¹⁹F-NMR (400 MHz, DMSO-d₆) δ -109.26 (quintet, J = 7.79 Hz, 1F), -113.53 (quartet, J = 9.23 Hz, 1F), -120.49 (d, J = 9.39 Hz, 2F). LC/MS t_r = 5.08 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 513 (M+H). ES-HRMS m/z 513.1177 (M+H calcd for C₂₄H₂₂ClF₄N₂O₄ requires 513.1199).

Example 357



N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-1-hydroxycyclopropanecarboxamide

Step 1: Preparation of the title compound

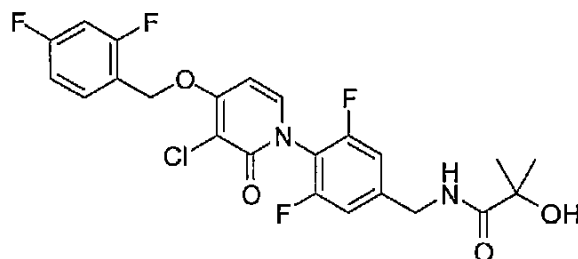
The compound was prepared following the procedure for , substituting 1-hydroxy-1-cyclopropanecarboxylic acid for 4-

imidazolecarboxylic acid. ¹H-NMR (400 MHz, DMSO-d₆) δ 8.70 (t, J = 6.26 Hz, 1H), 7.89 (d, J = 6.31, 1H), 7.65 (qr, J = 6.83, 1H), 7.34 (t, J = 10.58 Hz, 1H), 7.19 (m, 3H), 6.77 (d, J = 7.70 Hz, 1H), 5.38 (s, 2H), 4.35 (d, J = 5.66, 2H), 1.14 (s, 1H), 1.02 (m, 2H), 0.84 (m, 2H). ¹⁹F-NMR (400 MHz, DMSO-d₆) δ -109.25 (quintet, J = 8.05 Hz, 1F), -113.53 (quartet, J = 8.27 Hz, 1F), -120.59 (d, J = 8.99 Hz, 2F). LC/MS t_r = 5.01 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C)

ES-MS m/z 497 (M+H). ES-HRMS m/z 497.0873 (M+H calcd for $C_{23}H_{18}ClF_4N_2O_4$ requires 497.0886).

Example 358

5



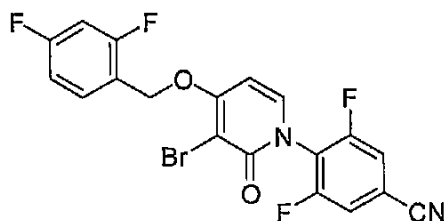
10 N-{4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzyl}-2-hydroxy-2-methylpropanamide

Step 1: Preparation of the title compound

The compound was prepared following the procedure for , substituting 2-hydroxyisobutyric acid for 4-

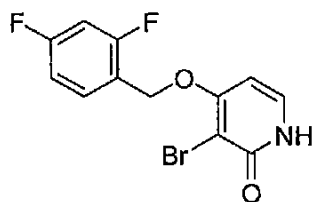
15 imidazolecarboxylic acid. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 8.48 (t, $J = 6.41$ Hz, 1H), 7.89 (d, $J = 7.78$, 1H), 7.65 (qr, $J = 9.10$, 1H), 7.33 (dt, $J = 10.12$, 2.41 Hz, 1H), 7.17 (m, 3H), 6.77 (d, $J = 7.69$ Hz, 1H), 5.38 (s, 2H), 4.31 (d, $J = 6.50$, 2H), 1.41 (s, 1H), 1.33 (s, 6H). $^{19}\text{F-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ -109.25
20 (quintet, $J = 7.49$ Hz, 1F), -113.53 (quartet, $J = 9.64$ Hz, 1F), -120.59 (d, $J = 8.68$ Hz, 2F). LC/MS $t_r = 5.05$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 499 (M+H). ES-HRMS m/z 499.1020 (M+H calcd for
25 $C_{23}H_{20}ClF_4N_2O_4$ requires 499.1042).

Example 359



4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-
 3,5-difluorobenzonitrile

Step 1: Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one .



The compound was prepared in the following the produre for 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (, Step 3), substituting *N*-bromosuccinimide for *N*-chlorosuccinimide.

¹H-NMR (400 MHz, DMSO-*d*₆) δ 11.85 (br s, 1H), 7.61 (m, 1H), 7.46 (d, *J* = 7.36 Hz, 1H), 7.30, (m, 1H), 7.14 (m, 1H), 6.40 (d, *J* = 7.71 Hz, 1H), 5.26 (s, 2H). ¹⁹F-NMR (400 MHz, DMSO-*d*₆) δ -109.69 (quintet, *J* = 7.93 Hz, 1F), -113.63 (quartet, *J* = 9.55 Hz, 1F). LC/MS *t*_r = 4.48 minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS *m/z* 316 (M+H).

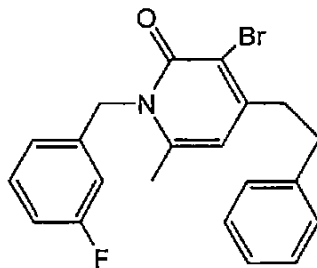
Step 2: Preparation of the title compound .

The compound was prepared following the procedure for 4-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-2-oxopyridin-1(2H)-yl]-3,5-difluorobenzonitrile (, Step 4), substituting 3-bromo-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (from step 1) (1.92 g,

6.06 mmol) for 3-chloro-4-[(2,4-difluorobenzyl)oxy]pyridin-2(1H)-one (, from Step 3). $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ 8.13 (d, $J = 7.24$ Hz, 2H), 7.95 (d, $J = 7.76$ Hz, 1H), 7.66 (quartet, $J = 8.71$ Hz, 1H), 7.34, (dt, $J = 9.94$, 2.53 Hz, 1H), 7.17 (dt, $J = 8.64$, 2.33 Hz, 1H), 6.82 (d, $J = 7.77$ Hz, 1H), 5.39 (s, 2H). $^{19}\text{F-NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ -109.28 (quintet, $J = 7.98$ Hz, 1F), -113.45 (quartet, $J = 9.29$ Hz, 1F), -116.30 (d, $J = 7.44$ Hz, 2F). LC/MS $t_r = 5.48$ minutes (0-95% acetonitrile/water, 0.05% trifluoroacetic acid, over 6 minutes at 1 ml/min with detection at 215 nm, at 50°C) ES-MS m/z 453 ($M+H$). ES-HRMS m/z 452.9836 ($M+H$ calcd for $\text{C}_{19}\text{H}_{10}\text{BrF}_4\text{N}_2\text{O}_2$ requires 452.9856).

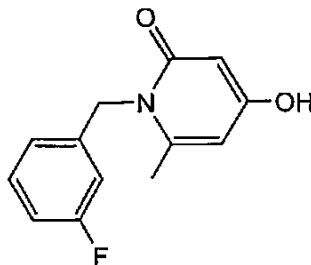
Example 360

15



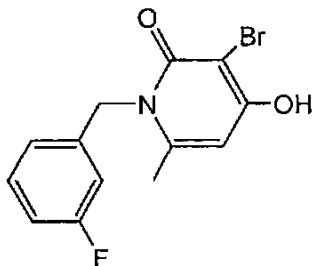
3-Bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one

20 Step 1: Preparation of 1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one



A mixture of 4-hydroxy-6-methyl-2-pyrone (2.5 g, 0.02 mol) and 3-fluorobenzylamine (2.5 g, 0.02 mol) in n-butanol (15.0 mL) was heated to reflux for 16 h under argon atmosphere. Butanol was distilled in vacuo, the residue was triturated with EtOAc, cooled and filtered the precipitate. It was washed with cold EtOAc, and dried to give 0.86 g of the title compound as a pale yellow powder: $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 7.31 (m, 1H), 7.0 - 6.85 (m, 2H), 6.83 (d, 1H, $J = 9.6\text{ Hz}$), 5.96 (d, 1H, $J = 2.0\text{ Hz}$), 5.80 (d, 1H, $J = 2.0\text{ Hz}$), 5.30 (s, 2H), and 2.24 (s, 3H); ESMS $m/z = 234$ (MH^+).

Step 2: Preparation of 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one

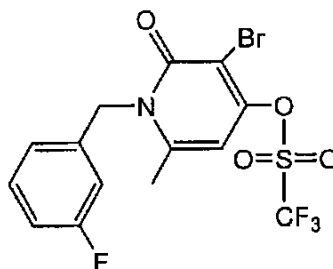


15

A mixture of 1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.8 g, 0.0034 mol), NBS (0.64 g, 0.0036 mol) in dichloromethane (15.0 mL) was stirred at room temperature, under argon atmosphere. After 1.5 h, the reaction mixture was diluted with dichloromethane (15.0 mL), cooled and filtered the solids. The residue was washed with dichloromethane and dried in vacuo to give 0.93 g of the title compound as a white powder: $^1\text{H-NMR}$ ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 7.33 (m, 1H), 7.2 - 6.8 (m, 3H), 6.07 (s, 1H), 5.34 (s, 2H), 2.26 (s, 3H); ESHRMS m/z 312.0016 ($\text{M}+\text{H}$ $\text{C}_{13}\text{H}_{12}\text{NO}_2\text{BrF}$ requires 312.0035).

25

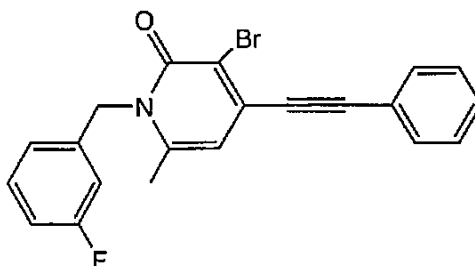
Step 3: Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate



To a suspension of 3-bromo-1-(3-fluorobenzyl)-4-hydroxy-6-methylpyridin-2(1H)-one

- 5 (0.86 g, 0.0028 mol) in dichloromethane (15.0 mL) cooled to -30 °C, triethyl amine (0.5 mL, 0.004 mol) and triflic anhydride (0.7 mL, 0.0042 mol) were added and stirred for 1 h. The resulting orange solution was poured into ice cold water (25 mL) and extracted with dichloromethane (2 x 25 mL). The
- 10 combined organic extracts were washed with water, dried (Na₂SO₄) and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography using 1:1 EtOAc/hexane v/v to afford 1.0 g (85%) the title compound as a light brown solid: ¹H- NMR
- 15 (CDCl₃/400 MHz) δ 7.32 (m, 1H), 7.0 - 6.85 (m, 3H), 6.18 (s, 1H), 5.32 (s, 2H), and 2.34 (s, 3H); ESHRMS m/z 443.9492 (M+H C₁₄H₁₁NO₄BrF₄S requires 443.9528).

- 20 Step 4: Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one



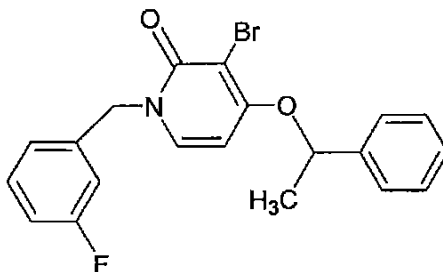
A solution of 3-bromo-1-(3-fluorobenzyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (1.0 g, 0.0022 mol) and phenylacetylene (0.3 mL, 0.0029 mol) in DMF (5.0 mL) was degassed using house vacuum, and purged with argon (3
5 cycles).

Then added diisopropylethylamine, (0.5 mL) followed by the addition of PdCl₂(PPh₃)₂ (0.36 g). The reaction mixture was heated at 65 °C for 1.5 h under argon atmosphere. The solvents were distilled in vacuo, and the residue was purified by
10 silica gel flash chromatography using EtOAc/hexane (2:3 v/v) to afford 0.65 g (70%) of the title compound as a brown colored amorphous solid: ¹H- NMR (CD₃OD/400 MHz) δ 7.59 (m, 2H), 7.45 - 7.3 (m, 4H), 7.05 - 6.85 (m, 3H), 6.44 (s, 1H), 5.41 (s, 2H), and 2.31 (s, 3H); ¹⁹F-NMR (CD₃OD/400 MHz) δ -
15 116.33 (m); ESHRMS m/z 396.0373 (M+H C₂₁H₁₆NOBrF 396.0399).

Step 5: Preparation of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(2-phenylethyl)pyridin-2(1H)-one

To a solution of 3-bromo-1-(3-fluorobenzyl)-6-methyl-4-(phenylethynyl)pyridin-2(1H)-one (0.55 g, 0.0014 mol) in
20 EtOAc (10.0 mL) and EtOH (10.0 mL) was added PtO₂ (0.05g) and stirred in an atmosphere of hydrogen gas at 15 psi for 30 min. The catalyst was removed by filtration, the filtrate was concentrated and the residue was purified by silica gel flash
25 chromatography using 25% EtOAc in hexane as the eluent. The appropriate fractions were combined (visualized under UV) and concentrated to dryness. ¹H- NMR (CD₃OD/400 MHz) δ 7.35 (m, 1H), 7.31 - 7.16 (m, 5H), 6.99 (m, 1H), 6.91 (m, 1H), 6.81 (m, 1H), 6.20 (s, 1H), 5.41 (s, 2H), 2.94 (m, 4H), and 2.24 (s,
30 3H); ¹⁹F-NMR (CD₃OD/400 MHz) δ -115.01 (m); ESHRMS m/z 400.0695 (M+H C₂₁H₂₀NOBrF 400.0712).

Example 361

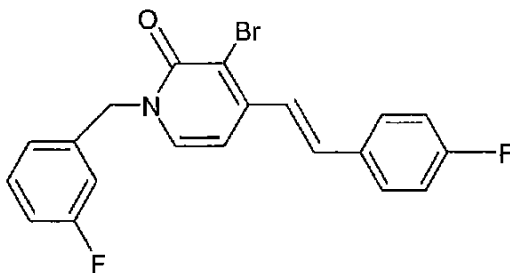


3-bromo-1-(3-fluorobenzyl)-4-(1-phenylethoxy)pyridin-2(1H)-

one

A mixture of 3-bromo-1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (0.2 g, 0.72 mmol), potassium carbonate (0.1 g, 0.72 mmol) and (1-bromoethyl)benzene (0.19 g, 1 mmol) in DMF (3.0 mL) was stirred at room temperature for 16 h. DMF was distilled in vacuo, and the residue was purified by flash chromatography (EtOAc in hexane (1:3 v/v) to give pale yellow syrup. This material was further purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min), at flow rate of 100 mL/min. The appropriate fractions were combined, concentrated to a small volume (20 mL), added EtOAc (25 mL) and washed successively with satd. sod. bicarbonate, water, and dried (Na₂SO₄). EtOAc was removed under reduced pressure and residue was dried in vacuo to afford the title compound (0.15 g, 52%) as an amorphous substance: ¹H NMR (CD₃OD/ 400 MHz) δ 7.56 (d, 1H, J = 7.6 Hz), 7.4 - 7.2 (m, 5H), 7.0 (m, 3H), 6.28 (d, 1H, J = 7.6 Hz), 5.65 (m, 1H), 5.19 (d x d, 2H, J = 14.8 Hz), and 1.64 (d, 3H, J = 6.4 Hz), ES-HRMS m/z 402.0492 (M+H C₂₀H₁₈NO₂Br, requires 402.0499).

Example 362

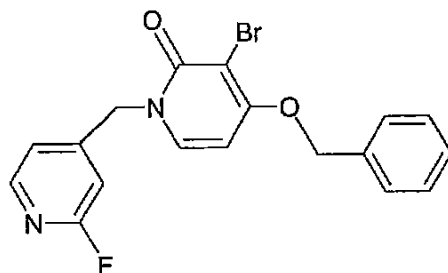


3-bromo-1-(3-fluorobenzyl)-4-[(E)-2-(4-fluorophenyl)ethenyl]pyridin-2(1H)-one

5 A mixture of 3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (1.0 g, 0.0023 mol), and 4-fluorostyrene (0.33 mL, 0.0028 mol) in degassed DMF (10.0 mL) containing diisopropyl ethyl amine (0.37 g, 0.0029 mol) was treated with $\text{PdCl}_2(\text{PPh}_3)_2$ (0.32 g, 0.46 mmol) and heated at 65 °C under argon atmosphere for 16 h. DMF was
10 distilled in vacuo, and the residue was purified by flash chromatography (EtOAc/ hexane 1:4 v/v) to afford a yellow substance which was further purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min), at flow
15 rate of 100 mL/min. The appropriate fractions were combined, concentrated to a small volume (20 mL), added EtOAc (25 mL) and washed successively with satd. sod. bicarbonate, water, and dried (Na_2SO_4). EtOAc was removed under reduced pressure and residue was dried in vacuo to afford the title compound
20 (0.06 g, 6%) as yellow powder: ^1H NMR (CD_3OD / 400 MHz) δ 7.68 (m, 3H), 7.39 (m, 3H), 7.2 - 7.0 (m, 5H), 6.82 (d, 1H, J = 7.2 Hz), and 5.22 (s, 2H); ^{19}F NMR (CD_3OD / 400 MHz) δ -113.9 (m) and -115 (m); ES-HRMS m/z 402.0305 ($\text{M}+\text{HC}_{20}\text{H}_{15}\text{NOF}_2\text{Br}$, requires 402.0300).

25

Example 363



4-(Benzyloxy)-3-bromo-1-[(6-fluoropyridin-3-yl)methyl]pyridin-2(1H)-one

5

A mixture of 4-(benzyloxy)-3-bromopyridin-2(1H)-one (0.2 g, 0.00076 mol), 5-bromomethyl-2-fluoropyridine (0.25 g, 0.0013 mol) and pot. Carbonate (0.15 g, 0.0011 mol) in DMF (3.0 ml) was stirred at room temperature for 16 h under argon

10

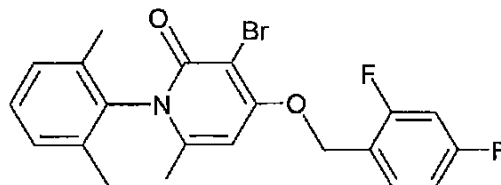
atmosphere. DMF was distilled in vacuo and the residue was partitioned between water (15 ml) and EtOAc (25 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. ^1H NMR (CD_3OD / 400

15

MHz) δ 8.22 (m, 1H, 2.4 Hz), 7.92 (m, 1H), 7.82 (d, 1H, J = 7.6 Hz), 7.44 - 7.31 (m 5H), 7.03 (m, 1H) 6.49 (d, 1H, J = 7.6 Hz), 5.29 (s, 2H), and 5.20 (s, 2H); ^{19}F NMR (CD_3OD / 400 MHz) δ -72.30 (d, J = 6.0 Hz) and -115 (m); ES-HRMS m/z 389.0295 ($M+H$ $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_2\text{FBr}$, requires 389.0309).

20

Example 364

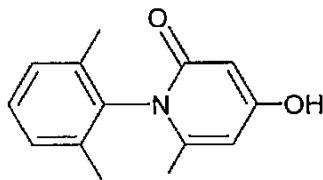


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1H)-one

25

STEP1

Preparation of



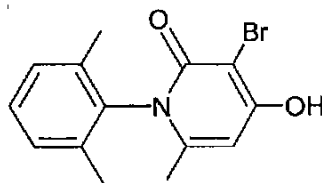
5 1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-
one

A mixture of 4-hydroxy-6-methyl-2-pyrone (2.5 g, 0.02 mol),
2,6 dimethylaniline (2.4 g, 0.02 mol), and p-toluenesulfonic
10 acid (0.2 g) as heated at 140 °C for 3 h under nitrogen
atmosphere. The reaction mixture was cooled, triturated
with acetonitrile, cooled and filtered the solids.

¹H NMR (CD₃OD/ 400 MHz) δ 7.22 (m, 3H), 6.12 (d, 1H, J = 1.6
Hz), 5.83 (d, 1H, J = 1.8 Hz), 2.00 (s, 6H), and 1.82 (s,
15 3H); ESMS m/z 229 (M+H).

Step 2

Preparation of



20 3-Bromo-1-(2,6-dimethylphenyl)-4-hydroxy-6-
methylpyridin-2(1H)-one

A mixture of 1-(2,6-dimethylphenyl)-4-hydroxy-6-
25 methylpyridin-2(1H)-one (0.4 g, 0.00175 mol), and NBS (0.35
g, 0.0019 mol) in dichloromethane (10.0 ml) was stirred at
room temperature under nitrogen atmosphere. After 1 h, the

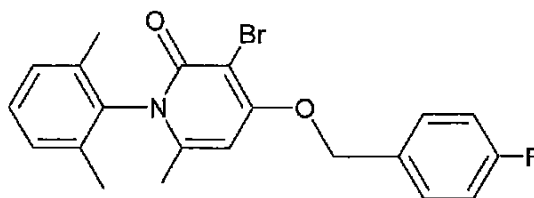
solids were filtered, washed with dichloromethane to give 0.42 g (78%) of the title compd as a pale yellow powder: ^1H NMR (CD_3OD / 400 MHz) δ 7.22 (m, 3H), 6.21 (s, 1H), 1.99 (s, 6H), and 1.82 (s, 3H); ESMS m/z 308/310 ($M+H$).

5

Step 3

A mixture of 3-Bromo-1-(2,6-dimethylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.15 g, 0.00049 mol), 2,4
10 difluorobenzyl bromide (0.12 g, 0.00058 mol) and potassium carbonate (0.075 g, 0.00054 mol) in DMF 3.00 mL) was stirred at room temperature under argon atmosphere for 2h. It was then heated at 60 °C for 30 min and concentrated in vacuo. The residue was purified by flash chromatography. ^1H NMR
15 (CD_3OD / 400 MHz) δ 7.62 (m, 1H), 7.28 (m, 3H), 7.04 (m, 2H), 6.68 (s, 1H), 5.35 (m, 1H), 1.98 (s, 6H), and 1.92 (s, 3H); ES-HRMS m/z 434.0574 ($M+H$ $\text{C}_{21}\text{H}_{19}\text{NO}_2\text{F}_2\text{Br}$, requires 434.0562).

20 Example 365



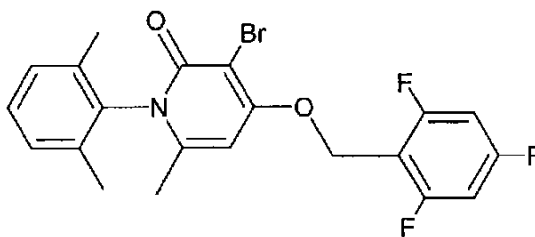
3-Bromo-1-(2,6-dimethylphenyl)-4-[(4-fluorobenzyl)oxy]-6-
25 methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to the one described for Example 364. ^1H NMR (CD_3OD / 400 MHz) δ 7.58 (m, 2H), 7.23 (m, 3H), 7.15 (m, 2H), 6.62 (s, 1H), 5.32

(s, 2H), 1.98 (m, 6H), and 1.91 (s, 3H); ES-HRMS m/z 416.0670. (M+H C₂₁H₂₀NO₂FBr, requires 416.0656).

Example 366

5

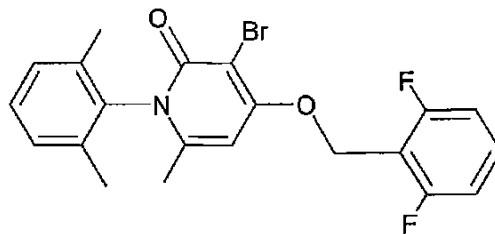


3-Bromo-1-(2,6-dimethylphenyl)-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1H)-one

10 The title compound was prepared by a procedure similar to the one described for EXAMPLE 364. ¹H NMR (CD₃OD/ 400 MHz) δ 7.19 (m, 3H), 6.95 (m, 2H), 6.69 (s, 1H), 5.29 (s, 2H), 1.95 (s, 6H), and 1.90 (s, 3H); ES-HRMS m/z 452.0471. (M+H C₂₁H₁₈NO₂F₃Br, requires 452.0468).

15

Example 367



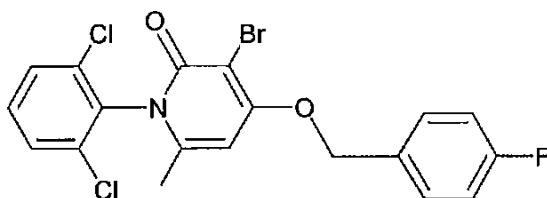
20

3-Bromo-4-[(2,6-difluorobenzyl)oxy]-1-(2,6-dimethylphenyl)-6-methylpyridin-2(1H)-one.

The title compound was prepared by a procedure similar to the one described for EXAMPLE 364. ¹H NMR (CD₃OD/ 400 MHz) δ

7.46 (m, 1H), 7.24 (m, 3H), 7.08 (m, 2H), 6.74 (s, 1H), 5.38 (s, 2H), 1.99 (s, 6H), and 1.94 (s, 3H); ES-HRMS m/z 434.0589 (M+H C₂₁H₁₉NO₂F₂Br, requires 434.0562).

5 Example 368

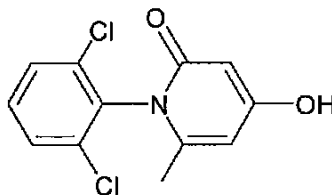


3-Bromo-1-(2,6-dichlorophenyl)-4-[(4-fluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

10

Step 1

Preparation of 1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



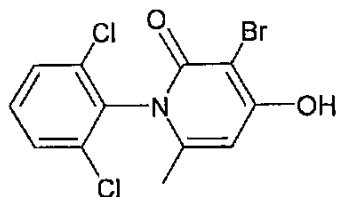
15

This compound was prepared by a procedure similar to the one described in step 1 for EXAMPLE 364. Yield: 28%, ¹H NMR (CD₃OD) δ 7.6 (m, 2H), 7.48 (m, 1H), 6.10 (dd, 1H), 5.78 (d, 1H, J = 2.4 Hz), 1.91 (s, 3H); (ES-MS m/z = 270 (MH⁺);

20

Step 2

Preparation of 3-bromo-1-(2,6-dichlorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



This compound was prepared by a procedure similar to the one described in step 2 for EXAMPLE 364. Yield: 78%, ^1H NMR (400

5 MHz) CD_3OD δ 7.61 (m, 2H), 7.49 (m, 1H), 6.2 (s, 1H), and 1.91 (s, 3H); ES-MS, m/z = 348 (MH^+).

Step 3

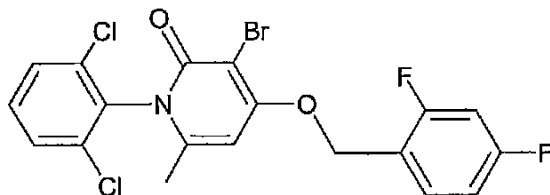
This compound was prepared by a procedure similar to the one

10 described in step 3 for EXAMPLE 364. Yield: 44%, ^1H NMR (CD_3OD)

δ 7.62 (d, 2H, J = 8.0 Hz), 7.51 (m, 3H), 7.15 (m, 2H), 6.64 (s, 1H), 5.33 (s, 2H), and 2.0 (s, 3H); ^{19}F NMR (CD_3OD) δ -166.21

(m); ES-HRMS m/z 455.9541 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{14}\text{NO}_2\text{Cl}_2\text{BrF}$, requires 455.9564).

15 Example 369



3-Bromo-1-(2,6-dichlorophenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

20

This compound was prepared by a procedure similar to the one described for EXAMPLE 368.

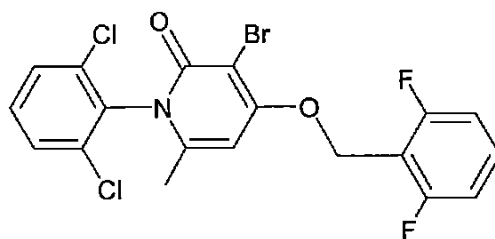
Yield: 64%, ^1H NMR (CD_3OD /400 MHz δ 7.62 (m, 3H), 7.48 (m, 1H), 7.05 (m, 2H), 6.70 (s, 1H), 5.36 (s, 2H), and 2.02 (s, 3H), ^{19}F NMR

25 (CD_3OD) δ -111.43 (m) and

-115.89 (m); ES-HRMS m/z 473.9450 (M+H C₁₉H₁₃NO₂Cl₂BrF₂, requires 473.9469).

Example 370

5

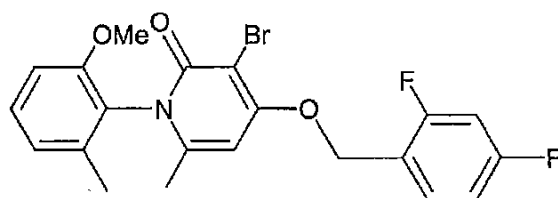


3-Bromo-1-(2,6-dichlorophenyl)-4-[(2,6-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

10 This compound was prepared by a procedure similar to the one described for EXAMPLE 368. Yield: 78%, ¹H NMR (CD₃OD/400 MHz) δ 7.62 (d, 2H, J = 8.0 Hz), 7.52 (m, 2H), 7.1 (m, 2H), 6.77 (s, 1H), and 2.04 (s, 3H); ¹⁹F NMR (CD₃OD) δ -117.04 (m); ES-HRMS m/z 473.9468 (M+H C₁₉H₁₃NO₂Cl₂BrF₂, requires 473.9469).

15

Example 371

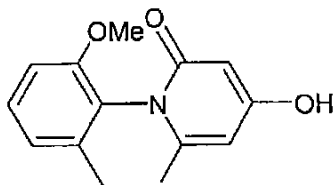


20 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one

Step 1

Preparation of 4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one

25

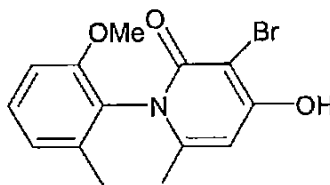


This compound was prepared by a procedure similar to the one described in step 1 for EXAMPLE 368. Yield: 21%, ^1H NMR

($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 7.31 (m, 1H), 6.94 (m, 2H), 6.05 (d, 1H, $J = 2.4\text{ Hz}$), 5.78 (d, 1H, $J = 2.4\text{ Hz}$), 3.76 (s, 3H), 2.00 (s, 3H), and 1.83 (s, 3H); ES-HRMS m/z 246.1092 ($\text{M}+\text{H}$ $\text{C}_{14}\text{H}_{16}\text{NO}_3$, requires 246.1123).

10 Step 2

Preparation of 3-bromo-4-hydroxy-1-(2-methoxy-6-methylphenyl)-6-methylpyridin-2(1H)-one



15

This compound was prepared by a procedure similar to the one described in step 2 for EXAMPLE 368. Yield: 58%, ^1H NMR

($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 7.34 (m, 1H), 6.96 (m, 2H), 6.15 (s, 1H), 3.76 (s, 3H), 1.99 (s, 3H), and 1.83 (s, 3H); ESMS m/z 324 ($\text{M}+\text{H}$).

20

Step 3

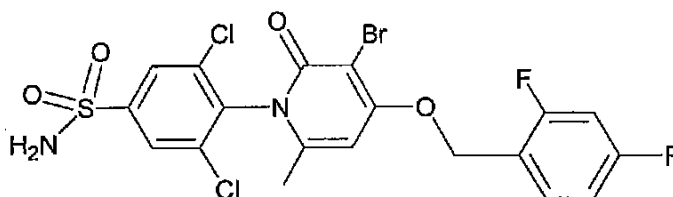
This compound was prepared by a procedure similar to the one described for EXAMPLE 368. Yield: 60%, ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$)

δ 7.63 (m, 1H), 7.36 (m, 1H), 7.01 (m, 4H), 6.61 (s, 1H), 5.33 (s, 2H), 3.76 (s, 3H), 1.99 (s, 3H), and 1.95 (s, 3H); ^{19}F NMR

(CD₃OD/400 MHz) δ -111.64 (m), and -116.03 (m); ES-HRMS m/z 450.0532 (M+H C₂₁H₁₉NO₃Cl₂BrF₂, requires 450.0511).

Example 372

5



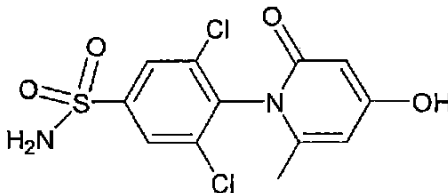
4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3,5-dichlorobenzenesulfonamide

10

Step 1

Preparation of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide

15



A mixture of 4-hydroxy-6-methylpyrone ((1.2 g, 0.0095 mol), and 2,6-dichlorosulphanilamide (2.4 g, 0.0099 mol) was heated at 170 °C under argon for 20 min. The resulting dark colored melt was cooled and the crude material was first purified by flash chromatography (EtOAc) to give partially purified material which contained the desired product. This was further purified by reverse-phase HPLC using 10 - 90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 349)were combined and freeze

dried to afford 0.19 g of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide as pale yellow solid:

^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 8.06 (s, 2H), 6.13 (d, 1H, $J = 1.6\text{ Hz}$), 5.78 (d, 1H, $J = 1.6\text{ Hz}$), and 1.94 (s, 3H); ES-HRMS m/z

5 348.9819 ($\text{M}+\text{H}$ $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_4\text{SCl}_2$ requires 348.9811).

Step 2

A mixture of 3,5-dichloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide (0.18 g, 0.0005 mol), N-

10 bromosuccinimide (0.1 g, 0.00056 mol) in acetic acid (2.0 mL)

was stirred at room temperature under argon atmosphere for 1 h. Acetic acid was removed in vacuo, the residue was

dissolved in DMF (2.0 mL), and added 2,4-difluorobenzyl

bromide (0.128 g, 0.0006 mol), potassium carbonate (0.1 g,

15 0.0007 mol). The resulting mixture was stirred at room temperature for 1 h. The solvents were distilled in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane 1: 3 v/v) to give 0.14 g of partially purified product.

This was further purified by reverse-phase HPLC using 10 - 90%

20 $\text{CH}_3\text{CN}/\text{Water}$ (30 min gradient) at a flow rate of 100 mL/min.

The appropriate fractions ($m/z = 553$) were combined and

freeze dried to afford 0.045 g of pale yellow powder. This

was partitioned between EtOAc (25 mL) and 5% sod. bicarbonate.

The organic phase was washed with water, dried (Na_2SO_4) and

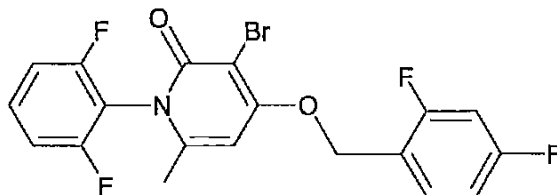
25 concentrated under reduced pressure. This material was dried in vacuo to afford the title compound (0.033 g) as a white amorphous substance:

^1H NMR ($\text{CDCl}_3/400\text{ MHz}$) δ 7.99 (s, 2H), 7.59 (m, 1H), 6.98 (m, 1H), 6.85 (m, 1H), 6.23 (s, 1H), 5.69 (s, 2H), 5.28 (s, 2H), 1.97

30 (s, 3H), and 1.76 (br, 2H); ES-HRMS m/z 552.7214 ($\text{M}+\text{H}$

$\text{C}_{19}\text{H}_{14}\text{BrCl}_2\text{N}_2\text{O}_4\text{S}$ requires 552.9197).

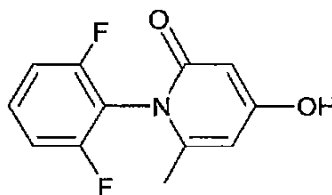
Example 373



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-
 5 6-methylpyridin-2(1H)-one

Step 1

Preparation of 1-(2,6-difluorophenyl)-4-hydroxy-6-
 10 methylpyridin-2(1H)-one

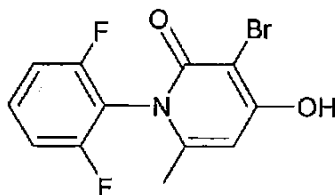


A mixture of 4-hydroxy-6-methyl-2-pyrone (10.0 g, 0.079 mol)
 15 and 2,6 difluoroaniline (9.5 g, 0.073 mol) was heated at 170
 °C under argon atmosphere for 20 min. The water formed was
 removed using a Dean-stark apparatus. The melt was cooled,
 the dark solid was triturated with EtOAc., and filtered. This
 material was washed thoroughly with EtOAc to afford the
 20 desired product 1-(2,6-difluorophenyl)-4-hydroxy-6-
 methylpyridin-2(1H)-one 6.5 g (35%) as a light brown solid: ¹H
 NMR (CD₃OD/400 MHz) δ 7.56 (m, 1H), 7.19 (m, 2H), 6.09 (m, 1H),
 5.77 (d, 1H, J = 2.4 Hz), and 1.99 (s, 3H); ES-HRMS m/z
 238.0679 (M+H C₁₂H₁₀NO₂F₂ requires 238.0674).

25

Step 2

Preparation of 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



5 The title compound was prepared by a procedure described in step2 for EXAMPLE 364.

Yield: 79%, ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 7.58 (m, 1H), 7.21 (m, 2H), 6.19 (d, 1H, $J = 0.8\text{ Hz}$), 1.99 (s, 3H); ES-HRMS m/z 315.9811 ($\text{M}+\text{H}$ $\text{C}_{12}\text{H}_9\text{NO}_2\text{F}_2\text{Br}$ requires 315.9779).

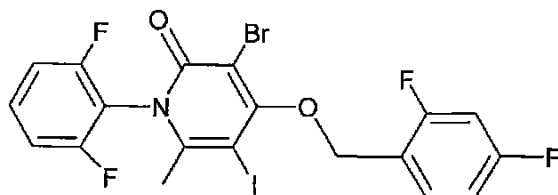
10

Step 3

This compound was prepared by a procedure described in step 3 for EXAMPLE 364.

15 Yield : 63%, ^1H NMR (CD_3OD) δ 7.58 (m, 2H), 7.23 (m, 2H), 7.06 (m, 2H), 6.68 (s, 1H), 5.36 (s, 2H), and 2.10 (s, 3H); ^{19}F NMR (CD_3OD) δ -111.50(m), -115.96(m), and -121.93 (m); ES-HRMS m/z 442.0061 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{13}\text{NO}_2\text{F}_4\text{Br}$ requires 442.0060).

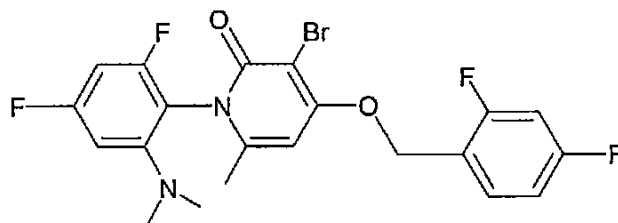
20 Example 374



25 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

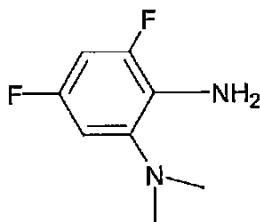
A solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (0.3 g, 0.00068 mol) and N-iodosuccinimide (0.22 g, 0.00098 mol) in dichloroethane, containing dichloroacetic acid (0.1 mL) was heated to reflux
5 for 6 h under argon atmosphere. After the removal of the solvents under reduced pressure, the residue was partitioned between, dichloromethane (20 mL) and 5% sod. sulphite (10 mL). The organic phase was washed with water, dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified
10 by flash chromatography (25% EtOAc in hexane) to afford the title compound (0.125 g, 32 %) as a pale yellow powder: ¹H NMR (CDCl₃/400 MHz) δ 7.68(m, 1H), 7.46 (m, 1H), 7.11 (m, 2H), 6.95 (m, 1H), 6.85 (m, 1H), 5.23 (s, 2H), and 2.38 (s, 3H); ¹⁹F NMR (CDCl₃) δ -109.15(m), -112.95 (m), -118.50 (m); ES-HRMS m/z
15 567.9014 (M+H C₁₉H₁₂NO₂F₄BrI requires 567.9027).

Example 375



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-(dimethylamino)-4,6-difluorophenyl]-6-methylpyridin-2(1H)-one

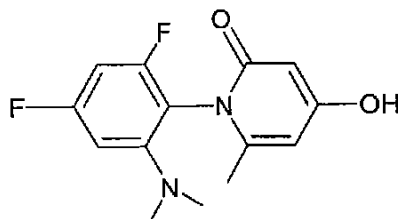
25 Step 1



3,5-difluoro-N,N-dimethylbenzene-1,2-diamine

To a solution of 2,4,6-trifluoronitrobenzene (2.58 g, 0.0145
 5 mol) in THF (20.0 ml) was added a solution of N,N-
 dimethylamine in THF (8.5 mL of 2M soln) and stirred for 45
 min at 0 °C. It was then stirred at room temperature for 30
 min and concentrated to dryness. The resulting material was
 dissolved in EtOH (25 mL), added Pd/C (10%, 0.6 g) and
 10 hydrogenated at 50 psi for 4 h. The catalyst was removed by
 filtration, and the filtrate was concentrated to dryness under
 reduced pressure. The residue was partitioned between sod.
 bicarbonate (10%, 25 mL) and EtOAc (30 mL). The organic phase
 was washed with water, dried (Na₂SO₄), and concentrated to
 15 dryness to afford the title compound (1.3 g, 50%) as a dark
 colored solid: ¹H NMR (CDCl₃/400 MHz) δ 6.52 (m, 2H), 3.64 (br,
 2H), and 2.65 (s, 6H); ES-HRMS m/z 172.0772 (M+ C₈H₁₀N₂F₂
 requires 172.0810).

20 Step 2



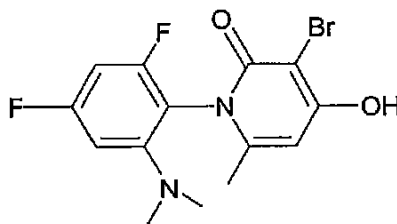
1-[2-(dimethylamino)-4,6-difluorophenyl]-4-hydroxy-6-methylpyridin-2(1H)-one

25

An intimate mixture of 4-hydroxy-6-methyl-2-pyrone (1.3 g, 0.0103 mol), and 3,5- difluoro-N,N-dimethylbenzene-1,2-diamine (1.4 g, 0.008 mol) was heated at 160 °C under argon for 15 min. The dark colored reaction mixture was cooled, triturated with EtOAc (15 ml), and filtered. The solids were washed with warm EtOAc, followed by hexane and dried to give the title compound as a light blue solid (0.4 g, 14 %). Analytically pure sample was prepared by reverse-phase HPLC purification using 10 -90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions were combined and freeze-dried to give the title compound: ¹H NMR (CD₃OD/400 MHz) δ 6.61 (m, 2H), 6.08 (d, 1H, J = 2.0 Hz), 6.78 (d, 1H, J = 2.0 Hz), 2.69 (s, 6H), and 1.94 (s, 3H); ES-HRMS m/z 281.1084 (M+H C₁₄H₁₅N₂O₂F₂ requires 281.1096).

Step 2

Preparation of



3-bromo-1-[2-(dimethylamino)-4,6-difluorophenyl]-4-hydroxy-6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure described in step2 for EXAMPLE 364. Yield:71%, ¹H NMR (CD₃OD/400 MHz) δ 6.62 (m, 2H), 6.17 (s, 1H), 2.67 (s, 6H), and 1.94 (s, 3H); ES-HRMS m/z 359.0188 (M+H C₁₄H₁₄N₂O₂F₂Br requires 359.0201).

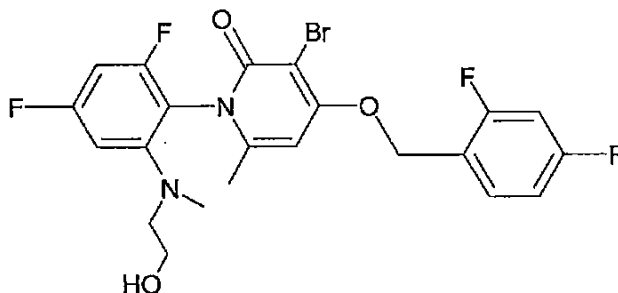
Step 3

This compound was prepared by a procedure described in step 3 for EXAMPLE 364.

Yield : 34%, ^1H NMR ($\text{CDCl}_3/400$ MHz) δ 7.62 (m, 1H), 6.98 (m, 1H), 6.85 (m, 1H), 6.46 (m, 2H), 6.11 (s, 1H), 5.24 (s, 2H), 2.66 (s, 6H), and 1.98 (s, 3H); ^{19}F NMR ($\text{CDCl}_3/400$ MHz) δ -108.06 (m), -109.60 (m), -115.02 (m), and -116.01 (m); ES-HRMS m/z 485.0451 ($\text{M}+\text{H}$ $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_2\text{F}_4\text{Br}$ requires 485.0482).

10 The title compound was prepared by stirring a suspension of the product of step 3, above, (0.14 g) with 4N HCl in dioxane (0.7 mL) at room temperature for 30 min. The mixture was concentrated to dryness. ^1H NMR ($\text{CD}_3\text{OD}/400$ MHz) δ 7.62 (m, 1H), 7.02 (m, 2H), 6.65 (m, 3H), 5.34 (s, 2H), 2.66 (s, 6H), and 2.05 (s, 3H); ESMS m/z = 485.

Example 376

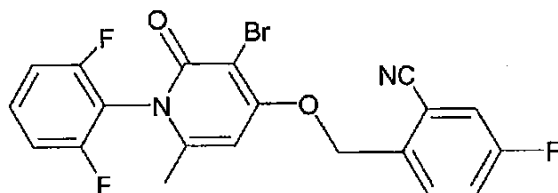


20 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2,4-difluoro-6-[(2-hydroxyethyl)(methyl)amino]phenyl)-6-methylpyridin-2(1H)-one

The title compound was prepared by a similar procedure described for EXAMPLE 375, replacing N,N-dimethyl group by N-Methyl-aminoethanol. ^1H NMR ($\text{CDCl}_3/400$ MHz) δ 7.59 (m, 1H), 6.98 (m, 1H), 6.85 (m, 1H), 6.61 (m, 1H), 6.52 (m, 1H), 6.17 (m, 1H), 5.25 (s, 2H), 3.63 (m, 1H), 3.53 (m, 1H), 3.26 (m, 1H),

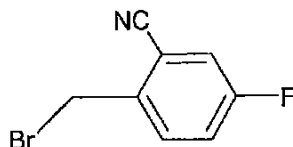
3.0 (m, 1H), 2.66 (s, 6H), and 2.09 (s, 3H); ES-HRMS m/z 515.0512 (M+H C₂₂H₂₀N₂O₃F₄Br requires 515.0588).

Example 377



2-((3-Bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy)methyl)-5-fluorobenzonitrile

Step 1



2-(Bromomethyl)-5-fluorobenzonitrile

A mixture of 5-fluoro-2-methylbenzonitrile (2.0 g, 0.015 mol), NBS (3.2 g, 0.018 mol) and benzoylperoxide (0.25 g) in carbontetrachloride (25.0 ml) was heated to reflux for 6 h, under argon atmosphere. The reaction mixture was cooled and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (5% EtOAc in hexane) to afford 2-(Bromomethyl)-5-fluorobenzonitrile

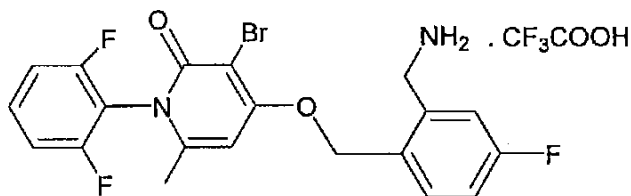
(1.9 g, 60%) as a colorless liquid: ¹H NMR (CDCl₃/400 MHz) δ 7.59 (m) 7.58 (m, 1H), 7.38 (m, 1H), and 7.25 (m, 1H).

Step 2

A mixture of 3-bromo-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one

1.0 g, 0.0032 mol), potassium carbonate (0.65 g, 0.0047 mol) and 2-(Bromomethyl) 5-fluorobenzonitrile (0.95 g, 0.0045 mol) in dimethylacetamide (15.0 ml) was stirred at room temperature under argon atmosphere. After 1h, dimethylacetamide was distilled in vacuo and the residue was partitioned between dichloromethane (50 ml) and 5% citric acid (15 mL). The organic phase was washed with water, dried (Na_2SO_4), and concentrated to dryness. The resulting material was triturated with EtOAc, filtered, washed with EtOAc and dried to afford the title compound (0.86 g, 60%) as a white powder: ^1H NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ 7.95(m, 1H), 7.81 (m, 1H), 7.68 (m, 2H), 7.37 (m, 2H), 6.79(s, 1H), 5.45 (s, 2H), and 2.03 (s, 3H); ^{19}F - NMR ($\text{DMSO}-d_6$) δ -111.31 (m), -120.34 (m); ES-HRMS m/z 449.0094 ($\text{M}+\text{H}$ $\text{C}_{20}\text{H}_{13}\text{N}_2\text{O}_2\text{F}_3\text{Br}$ requires 449.0107).

Example 378

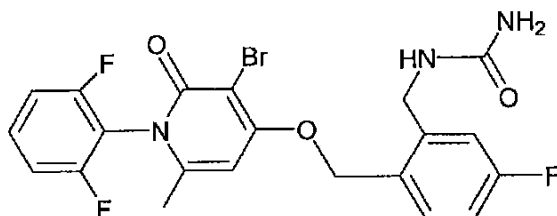


4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

To a cold suspension of 2-([3-Bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy)methyl)-5-fluorobenzonitrile (0.3 g, 0.00066 mol) in THF (3.0 mL), was added $\text{BH}_3\cdot\text{THF}$ (1.0 mL). After stirring at room temperature for 15 min, the reaction mixture was heated to reflux for 30 min under argon atmosphere. The resulting clear solution cooled,

added MeOH (2.0 mL), concentrated under reduced pressure, and the residue was purified by reverse-phase HPLC purification using 10 -90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 453 M+H) were
 5 combined and freeze-dried to give the title compound (0.16 g, 43%) as its trifluoroacetate salt: ¹H NMR (DMSO-d₆/400 MHz) δ 8.19 (br, 3H), 7.65 (m, 2H), 7.37 (m, 4H), 6.78 (s, 1H), 5.42 (s, 2H), 4.21 (br, 2H), and 2.04 (s, 3H); ¹⁹F NMR (DMSO-d₆/400 MHz) δ -112.96 (m), and -120.41 (m); ES-HRMS m/z 453.0387 (M+H
 10 C₂₀H₁₇N₂O₃F₃Br requires 453.0420).

Example 379

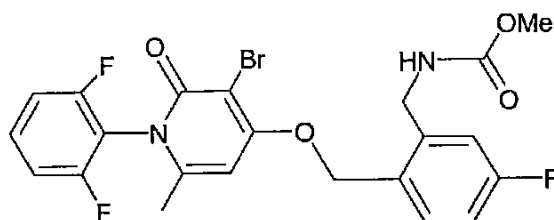


15 N-[2-([3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy)methyl]-5-fluorobenzyl]urea

To a suspension of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one
 20 trifluoroacetate (0.13g, 0.00023 mol) in THF (3.0 mL), was added triethyl amine (0.07 mL, 0.0005 mol) followed by the addition of trimethylsilylisocyanate (0.066 mL). The reaction mixture was stirred at room temperature for 1 h, and the desired product was isolated by reverse-phase HPLC
 25 purification using 10 -90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 496 M+H) were combined and freeze-dried, and the residue was partitioned between 5% sod. bicarbonate (20 mL) and dichloromethane (20

mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness under reduced pressure, to afford the title compound as a white amorphous powder (0.065 g): ^1H NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ 7.62 (m, 1H), 7.52 (m, 1H), 7.35 (m, 2H), 7.09 (m, 2H), 6.77 (s, 1H), 6.51 (t, 1H), 5.61 (s, 2H), 5.38 (s, 2H), 4.28 (d, 2H, $J = 6.0\text{ Hz}$), and 2.02 (s, 3H); ^{19}F NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ -114.044 (m), and -120.31 (m); ES-HRMS m/z 496.0460 ($\text{M}+\text{H}$ $\text{C}_{21}\text{H}_{18}\text{N}_3\text{O}_3\text{F}_3\text{Br}$ requires 496.0478).

Example 380



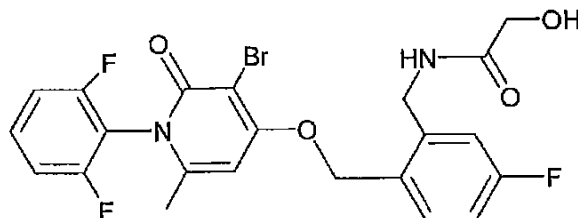
Methyl 2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

To solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.12g, 0.00021 mol) in dimethylacetamide (2.0 mL) at 0 °C, was added triethylamine (0.06 mL, 0.00043 mol) followed by the addition of methylchloroformate (0.05 mL). The reaction mixture was stirred at room temperature for 30 min under argon atmosphere. Dimethylacetamide was distilled in vacuo and the residue was partitioned between dichloromethane (10 mL) and 5% citric acid (10 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness. The resulting residue was purified by flash chromatography (60%EtOAc in hexane) to afford the title compound (0.09 g, 75%) as a white amorphous powder: ^1H NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ 7.68 (m, 1H), 7.62 (m, 1H), 7.59 (m, 1H),

7.38 (m, 2H), 7.115 (m, 2H), 6.78 (s, 1H), 5.38 (s, 2H), 4.31 (d, 2H, $J = 6.0$ Hz), 3.53 (s, 3H), and 2.03 (s, 3H); ^{19}F NMR (DMSO- d_6 /400 MHz) δ -113.77 (m), and -120.33 (m); ES-HRMS m/z 511.0508 ($M+H$ $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_4\text{F}_3\text{Br}$ requires 511.0475).

5

Example 381

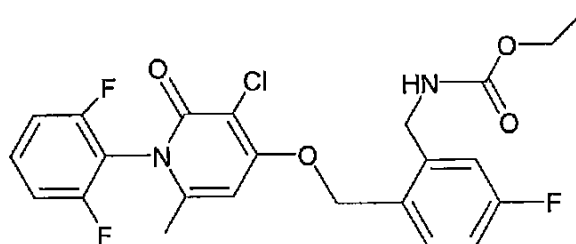


N-[2-({[3-bromo-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-
10 dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzyl]-2-
hydroxyacetamide

To a suspension of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-
bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one
15 trifluoroacetate (0.12g, 0.00021 mol) in
THF (2.0 mL) at 5 °C, was added triethyl amine (0.036 g,
0.00035 mol) followed by the addition of acetoxyacetyl
chloride (0.05 mL). The mixture was stirred at room
temperature for 30 min, diluted with cold water (10 mL), and
20 extracted the products with dichloromethane (2 x 10 mL). The
combined organic extracts were washed with water, dried
(Na_2SO_4) and concentrated to dryness. The residue was
dissolved in ethanol (0.5 mL), added 1N NaOH (0.5 mL) and
stirred at room temperature for 1 h. The resulting solution
25 was diluted with water (15 mL), and extracted with
dichloromethane (2 x 10 mL). The combined dichloromethane
extracts were washed with water, dried (Na_2SO_4) and
concentrated to dryness. The residue was purified by flash
chromatography (1% MeOH in EtOAc) to afford the title compound

(0.032 g, 30 %) as a white amorphous powder: ^1H NMR ($\text{CDCl}_3/400$ Hz) δ 7.45 (m, 2H), 7.18 (m, 1H), 7.05 (m, 3H), 6.23 (s, 1H), 5.24 (s, 2H), 4.56 (d, 2H, $J = 6.4$ Hz), 4.08 (d, 2H, $J = 5.2$ Hz), 2.79 (t, 1H), and 2.08 (s, 3H;) ^{19}F NMR ($\text{CDCl}_3/400$ MHz) δ -111.88 (m), and -118.62 (m); ES-HRMS m/z 511.0482 ($M+H$) $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_4\text{F}_3\text{Br}$ requires 511.0475).

Example 382



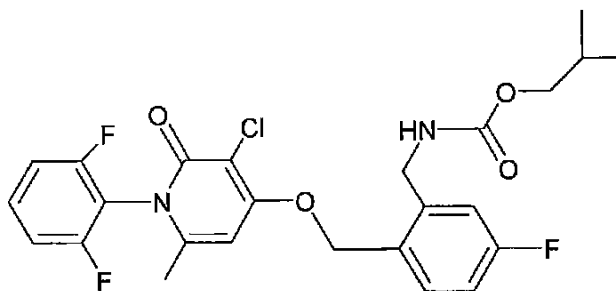
10

Ethyl 2-([3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy)methyl)-5-fluorobenzylcarbamate

To solution of 4-{[2-(aminomethyl)-4-fluorobenzyl]oxy}-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.3g, 0.00057 mol) in dimethylacetamide (3.0 mL) was added N-methylmorpholine (0.064 g, 0.00064 mol), followed by addition of ethylchloroformate (0.06 mL) and stirred at -10 $^{\circ}\text{C}$, for 30 min. The solvents were distilled in vacuo and the residue was purified by reverse-phase HPLC purification using 10 -90% $\text{CH}_3\text{CN}/\text{Water}$ (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions ($m/z = 481$ $M+H$) were combined and freeze-dried, and the residue was partitioned between 5% sod. bicarbonate (20 mL) and dichloromethane (20 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated to dryness under reduced pressure, to afford the title compound as a white amorphous powder (0.15 g, 55%): ^1H NMR ($\text{CD}_3\text{OD}/400\text{MHz}$) δ 7.61 (m, 1H), 7.52

(m, 1H), 7.26 (~t, 2H, J = 8.4 Hz), 7.12 (dd, 1H), 7.05 (3d, 1H, J = 2.4 Hz), 6.74 (s, 1H), 5.40 (s, 2H), 4.42 (s, 2H), 4.05 (q, 2H, J = 7.2 Hz), 2.12 (s, 3H), and 1.21 (t, 3H, J = 7.2 Hz); ES-HRMS m/z 481.1118 (M+H C₂₃H₂₁N₂O₄F₃Cl requires 481.1136).

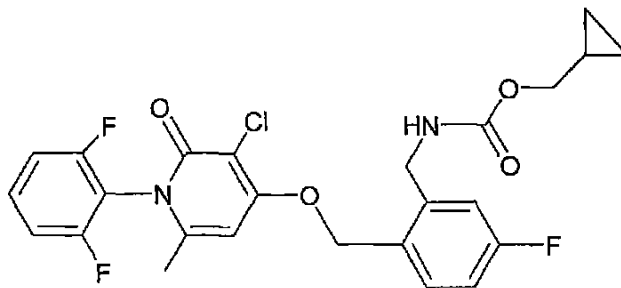
Example 383



Isobutyl 2-({[3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy}methyl)-5-fluorobenzylcarbamate

The title compound was prepared by a procedure similar to the one described for EXAMPLE 382. Yield 57 %; ¹H NMR (CD₃OD/400 MHz) δ 7.61 (m, 1H), 7.51 (m, 1H), 7.24 (~t, 2H, J = 8.0 Hz), 7.18 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.40 (s, 2H), 4.21 (s, 2H), 3.79 (d, 2H, J = 6.8 Hz), 2.12 (s, 3H), 1.85 (m, 1H), and 0.91 (d, 6H, J = 6.4 Hz); ES-HRMS m/z 509.1422 (M+H C₂₅H₂₅N₂O₄F₃Cl requires 509.1449)

Example 384



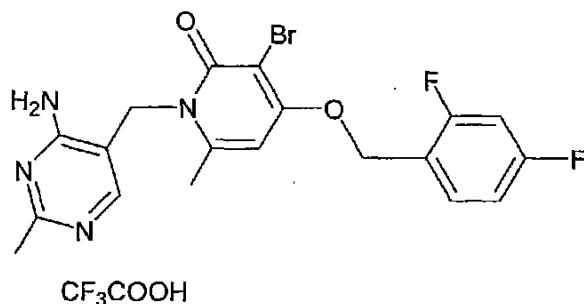
Cyclopropylmethyl 2-((3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl)oxy)methyl)-5-fluorobenzylcarbamate

5

The title compound was prepared by a procedure similar to the one described for EXAMPLE 382. Yield 46%; ^1H NMR ($\text{CD}_3\text{OD}/400\text{ Hz}$) δ 7.61 (m, 1H), 7.55 (m, 1H), 7.24 (~ t, 2H, $J = 7.6\text{ Hz}$), 7.18 (m, 1H), 7.05 (m, 1H), 6.73 (s, 1H), 5.40 (s, 2H), 4.42 (s, 2H), 3.83 (d, 2H, $J = 7.2\text{ Hz}$), 2.12 (s, 3H), 1.1 (br, 1H), 0.58 (~d, 2H), and 0.22 (~ d, 2H); ES-HRMS m/z 507.1316 ($M+H$ $\text{C}_{25}\text{H}_{23}\text{N}_2\text{O}_4\text{F}_3\text{Cl}$ requires 507.1293).

Example 385

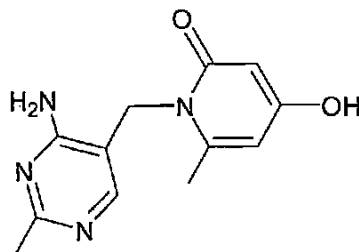
15



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

20

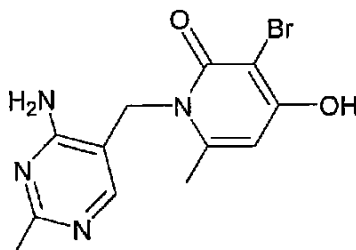
Step 1



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-hydroxy-6-methylpyridin-2(1H)-one

5 A mixture of 4-hydroxy-6-methyl-2-pyrone (0.9 g, 0.007 mol) and 4-amino-5-aminomethyl-2-methylpyrimidine (1.0 g, 0.007 mol) in water (10.0 ml) was heated at 100 °C for 1 h under argon atmosphere. The reaction mixture was cooled, and filtered the yellow precipitate. It was washed successively
 10 with cold water, ethanol, and dried in vacuo to afford the title compound (1.01 g, 51%) as a pale yellow powder: ¹H NMR (DMSO-d₆/400 MHz) δ 7.62 (s, 1H), 7.04 (s, 1H), 5.83 (d, 1H, J = 2.0 Hz), 5.58 (d, 1H, J = 2.0 Hz), 4.92 (s, 2H), 2.24 (s, 3H), and 2.22 (s, 3H); ES-HRMS m/z 325.0304 (M+H C₁₂H₁₄N₄O₂Br requires
 15 325.0295).

Step 2



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one
 20

A mixture of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-4-hydroxy-6-methylpyridin-2(1H)-one (0.5 g, 0.002 mol), and NBS (0.4 g, 0.002 mol) in glacial acetic acid (5.0 ml) was stirred

at room temperature for 1 h under argon atmosphere. Acetic acid was removed in vacuo, residue was triturated with EtOAc containing 10 % EtOH, and filtered. The pale yellow precipitate was washed with EtOAc containing 10% EtOH and dried in vacuo to afford the title compound (0.47 g, 725) as a pale yellow powder:

^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 7.62 (s, 1H), 6.09 (s, 1H), 5.15 (s, 2H), 2.42 (s, 3H), and 2.33 (s, 3H); ES-HRMS m/z 247.1160 ($\text{M}+\text{H}$ $\text{C}_{12}\text{H}_{15}\text{N}_4\text{O}_2$ requires 247.1190).

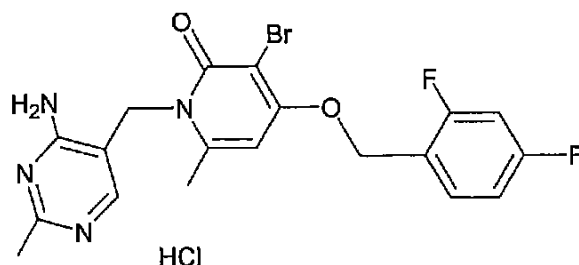
Step 3

To suspension of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-hydroxy-6-methylpyridin-2(1H)-one (1.0 g, 0.0031 mol)

and potassium carbonate (0.0 g, 0.004 mol) in dimethylacetamide (10.0 mL) was added 2,4 difluorobenzyl bromide (0.62 mL, 0.0048 mol) and stirred at room temperature for 2 hours. Dimethylacetamide was distilled in vacuo and the residue was purified by reverse-phase HPLC using 10 - 90%

$\text{CH}_3\text{CN}/\text{Water}$ (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions ($m/z = 566$) were combined and freeze dried to afford 0.65 g (37 %) of the title compound as its trifluoroacetate salt: ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 7.65 (s, 1H), 7.58 (m, 1H), 7.05 (m, 2H), 6.61 (s, 1H), 5.31 (s, 2H), 5.18 (s, 2H), 2.51 (s, 3H), and 2.46 (s, 3H); ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ -111.39 (m), and -115.98 (m); ES-HRMS m/z 451.0590 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_2\text{BrF}_2$ requires 451.0576).

Example 386

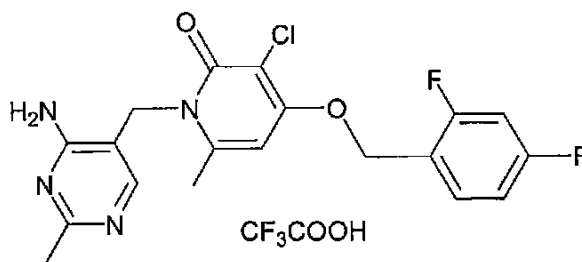


1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

5 Ion exchange (25g) BioRad AG 2X8 resin (200-400 mesh chloride form) was washed with 1M HCl (150 mL), and equilibrated for 2.5 h. This resin was loaded onto a column, and added a solution of Example 385 (3.3 g, 5.8 mmol) in water/CH₃CN (1:1). The column was eluted slowly over 1 h, fractions were
10 collected, and freeze dried to afford the desired HCl salt (2.2 g, 72%) as a white solid: ¹H-NMR (CD₃OD, 400Hz) δ 7.60 (m, 2H), 7.21 (m, 2H), 6.62 (s, 1H), 5.31 (s, 2H), 5.18 (s, 2H), 2.52 (s, 3H), 2.47 (s, 3H); ES-HRMS m/z 451.0544/453.0577 (M+H C₁₉H₁₇N₄O₂F₂Br requires 451.0581/453.0563).

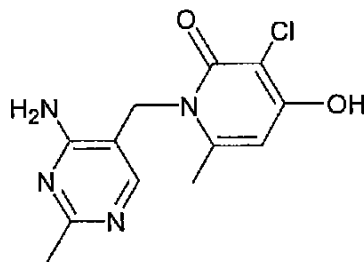
15

Example 387



1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate
20

Step 1. Preparation of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-hydroxy-6-methylpyridin-2(1H)-one



^1H NMR (CD_3OD , 400Hz) δ 7.62 (m, 1H), 6.11 (s, 1H), 5.13 (s, 2H), 2.66 (s, 3H), 2.42 (s, 3H); ES-HRMS m/z 281.0793 ($\text{M}+\text{H}$ $\text{C}_{12}\text{H}_{13}\text{N}_4\text{O}_2\text{Cl}$ requires 281.0800).

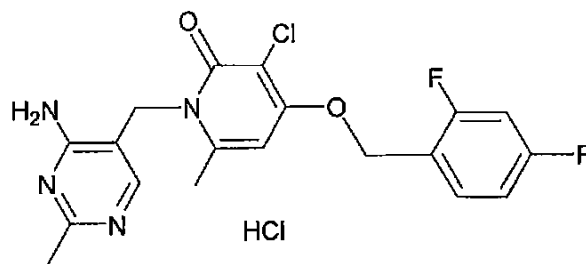
5

Step 2. Preparation of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate

10 The title compound was prepared by a procedure similar to the one described for Example 385 step 2. ^1H NMR (CD_3OD , 400Hz) δ 7.59 (m, 2H), 7.03 (m, 2H), 6.63 (s, 1H), 5.31 (s, 2H), 5.17 (s, 2H), 2.48 (s, 3H), 2.46 (s, 3H); ES-HRMS m/z 407.1097 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{17}\text{N}_4\text{O}_2\text{ClF}_2$ requires 407.1081).

15

Example 388

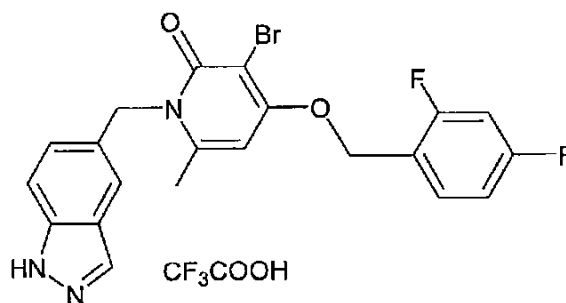


20 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride

Ion exchange (12.5g) BioRad AG 2X8 resin (200-400 mesh chloride form) was washed with 1M HCl (150 mL), and

equilibrated for 2.5 h. This resin was loaded onto a column, and added a solution of EXAMPLE 387 (1.2 g, 2.4 mmol) in water/CH₃CN (1:1). The column was eluted slowly over 1 h, fractions were collected, and freeze dried to afford the
 5 desired HCl salt (1.03 g, 97%) as a white solid: ¹H NMR (CD₃OD, 400Hz) δ 7.60 (m, 2H), 7.04 (m, 2H), 6.64 (s, 1H), 5.31 (s, 2H), 5.17 (s, 2H), 2.50 (s, 3H), 2.47 (s, 3H); ES-HRMS m/z 407.1079 (M+H C₁₉H₁₇N₄O₂ClF₂ requires 407.1081).

10 Example 389



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-(1H-indazol-5-ylmethyl)-6-methylpyridin-2(1H)-one trifluoroacetate

15

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.55 g, 0.0017 mol) and 5-(bromomethyl)-1-tetrahydro-2H-pyran-2-yl-1H-indazole (0.5 g, 0.0017 mol) in THF (10.0 mL) was added NaH (0.045 g, 0.0019
 20 mol) and heated at

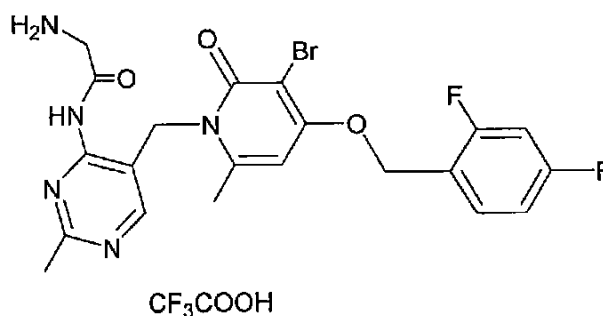
60 °C for 16 h under argon atmosphere. THF was distilled under reduced pressure, and the residue was suspended in EtOAc, added acetic acid (0.5 mL) and the product was purified by flash chromatography (80% EtOAc in hexane). The appropriate
 25 fractions were combined and concentrated to give an amorphous substance (0.31 g). This was stirred with trifluoroacetic (0.5 mL) for 30 min, the solution was diluted with acetonitrile (5 mL) and the product was isolated by reverse-

phase HPLC using 10 - 90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 460) were combined and freeze dried to afford 0.14 g (52%) of the title compound as its trifluoroacetate salt: ¹H NMR

(CD₃OD/400 MHz) δ 7.97 (s, 1H), 7.62 (m, 1H), 7.51 (m, 1H), 7.45 (s, 1H), 7.25 (m, 1H), 7.03 (t, 2H), 6.49 (s, 1H), 5.53 (s, 2H), 5.29 (s, 2H), and 2.40 (s, 3H); ¹⁹F NMR (CD₃OD/400 MHz) δ -111.69 (m), -116.09 (m); ES-HRMS m/z 460.0432 (M+H C₂₁H₁₇N₃O₂BrF₂ requires 460.0467).

10

Example 390

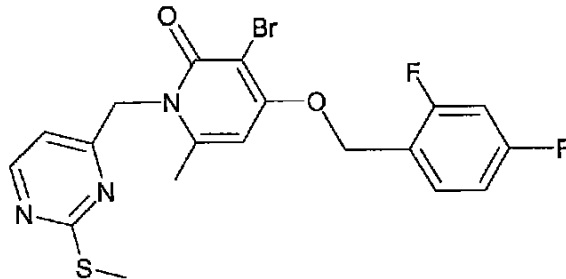


N-1-((5-([3-bromo-4-((2,4-difluorobenzyl)oxy)-6-methyl-2-oxopyridin-1(2H)-yl)methyl]-2-methylpyrimidin-4-yl)glycinamide trifluoroacetate

To a solution of BOC-Gly-OH (0.19 g, 0.0011 mol) in DMF (2.0 mL), was added N-methylmorpholine (0.14 mL, 0.0011 mol), followed by the addition of isobutylchloroformate (0.15 mL, 0.0011 mol) and stirred at -10 °C for 15 min. Then added a solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate (0.125 g, 0.00022 mol) in DMF (2.0 mL) containing diisopropylethylamine (0.1 g, 0.006 mL) and the resulting mixture was stirred for 16 h, at room temperature. The solvents were distilled in vacuo and the residue was

purified by reverse-phase HPLC using 10 - 90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 608/610) were combined and freeze dried to afford 0.025 g of white powder. This was stirred
 5 with trifluoroacetic acid (0.5 mL) for 1 h and product was isolated by reverse-phase HPLC using 10 - 90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 508/510) were combined and freeze dried to afford the title compound (0.02 g) as a white powder: ¹H NMR
 10 (CD₃OD/400 MHz) δ 8.18 (s, 1H), 7.61 (m, 1H), 7.02 (m, 2H), 6.59 (s, 1H), 5.30 (s, 4H), 4.23 (s, 2H), 2.60 (s, 3H), and 2.47 (s, 3H); ES-HRMS m/z 508.0797 (M+H C₂₁H₂₁N₅O₃BrF₂ requires 508.0790).

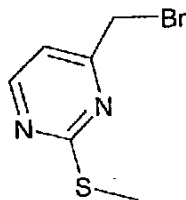
15 Example 391



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylthio)pyrimidin-4-yl]methyl}pyridin-2(1H)-one

20

Step 1



4-(Bromomethyl)-2-(methylthio)pyrimidine

To a solution of 4-methyl-2-methylthiopyrimidine (12.6 g, 0.09 mol) in acetic acid (50.0 mL) was added bromine (5.5 mL, 0.11 mol) and heated at 80 °C under argon atmosphere for 2 h.

Acetic acid was distilled in vacuo, the residue was triturated

5 with dichloromethane (100.0 mL) and poured into satd.

sod.bicarbonate solution (200.0 mL). Additional

dichloromethane (100.0 mL) was added and stirred for 15 min.

The organic phase was washed with water (3 x 100 mL), dried

(Na₂SO₄), and concentrated under reduced pressure. The dark

10 colored residue was purified by flash chromatography

(EtOAc/hexane 1:4 v/v) to afford 4-(bromomethyl)-2-

(methylthio)pyrimidine (10.9 g, 55%) as a dark colored liquid:

¹H NMR (CDCl₃/400 MHz) δ 8.50 (d, 1H, J = 4.8 Hz), 7.09 (d, 1H, J = 4.8 Hz), 4.34 (s, 2H), and 2.56 (s, 3H); ESMS m/z 219 (M+H).

15 Step 2

To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one 5.0 g, 0.015 mol) and 4-

20 (Bromomethyl)-2-(methylthio)pyrimidine (4.0 g, 0.018 mol) in THF (50.0 mL) was added NaH (0.4 g, 0.0017) and stirred at 55 °C under argon for 16 h. The reaction mixture was

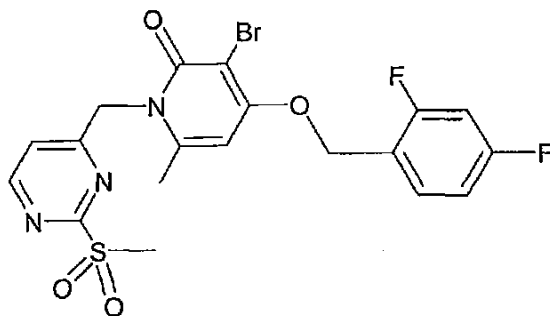
concentrated under reduced pressure and the residue was

partitioned between 5% citric acid (25 mL) and EtOAc (50 mL).

25 A precipitate was formed, it was filtered, washed with water, EtOAc, and dried in vacuo to afford the title compound

(4.2 g, 59 %) as a light brown powder, ¹H NMR (CD₃OD/400 MHz) δ 8.45 (d, 1H, J = 5.2 Hz), 7.6 (m, 1H), 7.06 (d over m, 2H, J = 5.2 Hz), 6.54 (s, 1H), 5.39 (s, 2H), 5.32 (s, 2H), 2.43 (s, 30 3H), 2.33 (s, 3H); ES-HRMS m/z 468.0173 (M+H C₁₉H₁₇N₃O₂BrSF₂ requires 468.0187).

Example 392

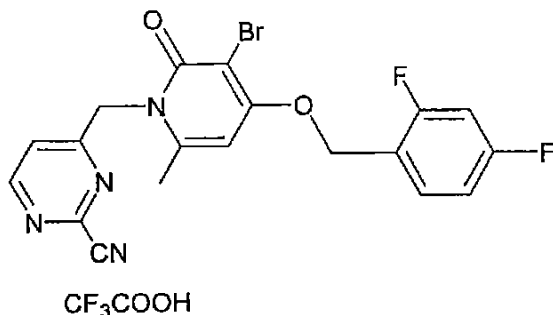


5

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[[2-(methylsulfonyl)pyrimidin-4-yl]methyl]pyridin-2(1H)-one

A suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[[2-(methylthio)pyrimidin-4-yl]methyl]pyridin-2(1H)-one 0.28 g, 0.0006 mol), and magnesium monoperoxyphthalate hexahydrate 90.6 g, 0.0012 mol) in acetonitrile (8.0 mL) and water (2.0 mL) was stirred at room temperature for 16 h. The resulting clear solution was concentrated under reduced pressure, and the residue was partitioned between dichloromethane (30 mL) and water (20 mL). The organic phase was washed with water, dried (Na₂SO₄) and concentrated to afford the title compound (0.27 g, 90%) as a pale yellow substance: ¹H NMR (CD₃OD/400 MHz) δ 8.91 (d, 1H, J = 5.2 Hz), 7.63 (d over m, 2H, J = 5.2 Hz), 7.03 (m, 2H), 6.58 (s, 1H), 5.54 (s, 2H), 5.33 (s, 2H), 3.28 (s, 3H), and 2.49 (s, 3H); ¹⁹F NMR (CD₃OD/400 MHz) δ -111.58 (m), -115.98 (m); ES-HRMS m/z 500.0113 (M+H C₁₉H₁₇N₃O₄BrSF₂ requires 500.0086).

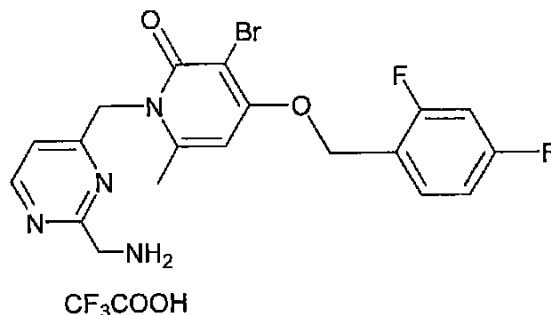
25 Example 393



4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile
 5 trifluoroacetate

A mixture of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[2-(methylsulfonyl)pyrimidin-4-yl]methyl}pyridin-2(1H)-one (1.0 g, 0.002 mol) and NaCN (0.15 g, 0.0031 mol) in DMF (5.0
 10 mL) was stirred at room temperature for 2 h under argon atmosphere. DMF was distilled in vacuo, the residue was triturated with acetonitrile (10 mL) and water (10 mL), and filtered the red colored precipitate. It was washed with acetonitrile and dried to afford the title compound (0.26 g).
 15 The washings and the filtrate were combined and purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min to give an additional 0.5 g of the title compound: ^1H NMR ($\text{CD}_3\text{OD}/400$ MHz) δ 8.83 (d, 1H, $J = 5.2$ Hz), 7.62 (d over m, 2H, $J = 5.2$ Hz), 7.00 (m, 2H), 6.58 (s, 1H), 5.46 (s, 2H), 5.33 (s, 2H), and 2.47 (s, 3H); ^{19}F NMR ($\text{CD}_3\text{OD}/400$ MHz) δ -111.64 (m), -116.03 (m); ES-HRMS m/z 447.0278 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{14}\text{N}_4\text{O}_2\text{BrF}_2$ requires 447.0263).
 20

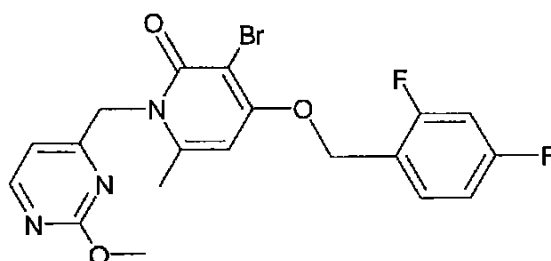
Example 394



4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

- 5 To a solution of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0.3 g, 0.00066mol) in a solvent mixture of EtOAc (15.0 mL) and acetic acid (5.0 mL), was added Pd/C (10 % , 0.18 g) and stirred in an atmosphere of hydrogen at 15 psi
- 10 for 2 h. The catalyst was removed by filtration . The filtrate was concentrated to dryness and the residue was residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions ($m/z = 451$) were combined
- 15 and freeze dried to afford (0.32 g, 645) of the title compound as its trifluoroacetate salt: ^1H NMR ($\text{DMSO}-d_6/400 \text{ MHz}$) δ 8.78 (d, 1H, $J = 5.2 \text{ Hz}$), 8.28 (br, 2H), 7.62 (m, 1H), 7.38 (m, 1H), 7.25 (d, 1H, $J = 5.2 \text{ Hz}$), 7.18 (m 1H), 6.62 (s, 1H), 5.32 (s, 2H), 5.29 (s, 2H), 4.24 (s, 2H), and 2.46 (s, 3H); ^{19}F NMR
- 20 ($\text{DMSO}-d_6/400 \text{ MHz}$) δ -109.59 (m), -113.67 (m); ES-HRMS m/z 451.0530 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_2\text{BrF}_2$ requires 451.0576).

Example 395



CF₃COOH

3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-methoxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

5

A solution of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0.13 g, 0.00023 mol) in MeOH (2.0 mL) was treated with 1N NaOH (0.5 mL). After stirring at room

10 temperature for 3h, it was heated at 60 °C for an additional 3 h and left overnight room temperature. The resulting solution was diluted with acetonitrile, and purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate

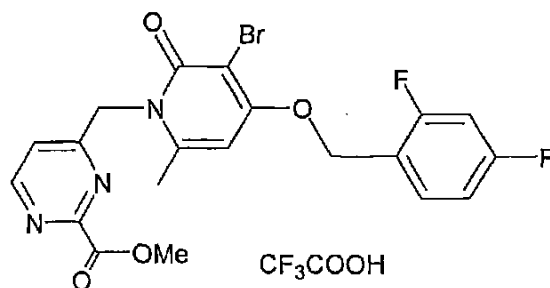
15 fractions (m/z = 452) were combined and freeze dried to afford the title compound (0.015 g) as a white powder: ¹H

NMR (CD₃OD) δ 8.84 (d, 1H, J = 5.2 Hz)

7.62 (d, 1H, J = 5.2 Hz), 7.05 (m, 2H), 6.57 (s, 1H), 5.49 (s, 2H), 5.32 (s, 2H), 3.96 (s, 3H), and 2.49 (s, 3H); ES-HRMS m/z

20 452.0440 (M+H C₁₉H₁₇N₃O₃BrF₂ requires 452.0416).

Example 396

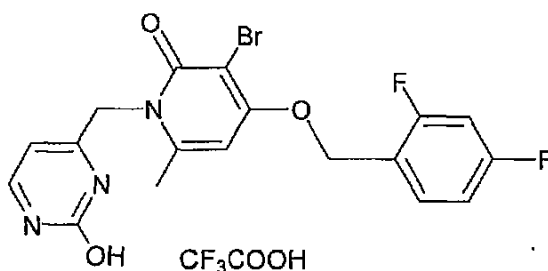


Methyl 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carboxylate trifluoroacetate

5

The title compound was obtained as a second product in the formation of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-methoxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate. ¹H NMR (CD₃OD/400 MHz) δ 8.46 (d, 1H, J = 5.2 Hz), 7.62 (m, 1H), 7.00 (m 2H), 6.93 (d, 1H, J = 5.2 Hz), 6.55 (s, 1H), 5.39 (s, 2H), 5.32 (s, 2H), 3.85 (s, 3H), and 2.44 (s, 3H); ES-HRMS m/z 480.0340 (M+H C₂₀H₁₇N₃O₄BrF₂ requires 480.0365).

15 Example 397



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(2-hydroxypyrimidin-4-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

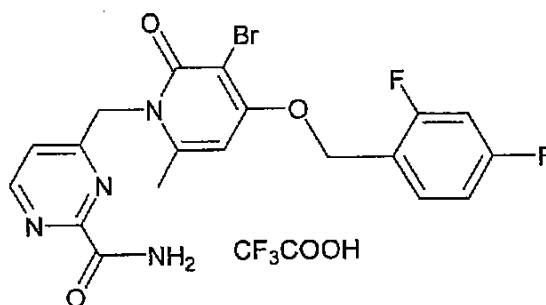
20

A mixture of 4-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carbonitrile trifluoroacetate (0.2 g, 0.00035 mol) potassium fluoride on

aluminum oxide (0.25 g) in t-butanol (5.0 mL) was refluxed for 4 h under argon atmosphere. The reaction mixture was cooled, filtered the precipitate and washed with ethanol. The combined filtrate and washings were concentrated to dryness and the residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions ($m/z = 452$) were combined and freeze dried to afford the title compound (0.05 g) as a white powder:

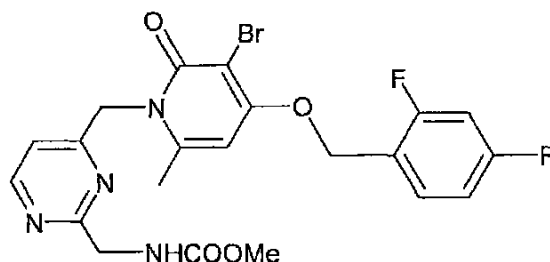
^1H NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ 7.85 (d, 1H $J = 6.4\text{ Hz}$), 7.64 (m, 1H), 7.30 (m 1H), 7.15 (m 1H), 6.55 (s, 1H), 6.22 (d, 1H, $J = 6.4\text{ Hz}$), 5.28 (s, 2H), 5.12 (d, 2H), and 2.29 (s, 3H); ^{19}F - NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ - 109.69 (m), and -113.67 (m); ES-HRMS m/z 438.0228 ($\text{M}+\text{H}$ $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3\text{BrF}_2$ requires 438.0259).

Example 398



4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidine-2-carboxamide trifluoroacetate

The title compound was obtained by a procedure described for Example 397. ^1H NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ 8.82 (d, 1H $J = 5.2\text{ Hz}$), 8.01 (br, 1H), 7.79 (br 1H), 7.64 (m, 1H), 7.34 (m, 2H), 7.16 (m 1H), 6.62 (s, 1H), 5.36 (s, 2H), 5.30 (s, 2H), and 2.38 (s, 3H); ^{19}F NMR ($\text{DMSO}-d_6/400\text{ MHz}$) δ - 109.64 (m), and -113.66 (m); ES-HRMS m/z 465.0385 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_3\text{BrF}_2$ requires 465.0368).



Example 399

Methyl (4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrimidin-2-yl)methylcarbamate

5

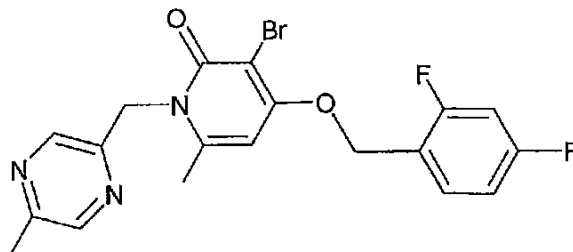
To a solution of 4-{[2-(Aminomethyl)-4-fluorobenzyl]oxy}-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate (0.13 g, 0.00023 mol) in dimethylacetamide (1.0 mL), was added triethylamine (0.04 mL, 0.0003 mol), followed by the addition of methylchloroformate (0.05 mL) and stirred at 0 °C for 30 min under argon atmosphere. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water, dried (Na₂SO₄) and concentrated to dryness.

15 The resulting residue was purified by flash chromatography (5% MeOH in EtOAc) to afford the title compound (0.055 g, 37%) as pale yellow powder: ¹H NMR (DMSO-d₆/400 MHz) δ 8.65 (d, 1H J = 5.6 Hz), 7.63 (1H), 7.5 (m, 1H), 7.28 (m 1H), 7.13 (m, 2H), 6.59 (s, 1H), 5.28 (s, 4H), 5.26 (d, 2H, J = 6.0 Hz), and 2.46 (s, 3H); ¹⁹F NMR (DMSO-d₆/400 MHz) δ - 109.64 (m), and -113.71 (m); ES-HRMS m/z 509.0621 (M+H C₂₁H₂₀N₄O₄BrF₂ requires 509.0630).

20

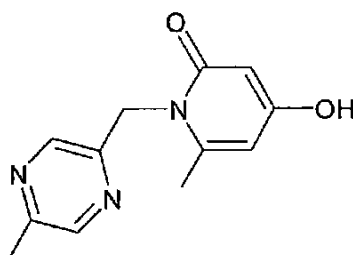
Example 400

25



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

5 Step 1

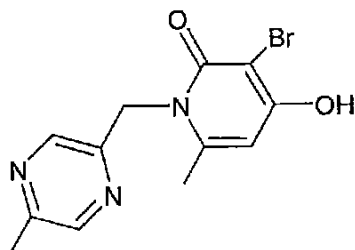


4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

10 A mixture of 4-hydroxy-6-methyl-2-pyrone (5.0 g, 0.04 mol) and 5-aminomethyl-2-methylpyrazine (5.0 g, 0.041 mol) in water (25.0 ml) was heated at 100 °C for 1 h under argon atmosphere. The reaction mixture was cooled, and filtered the yellow precipitate. It was washed with ethanol, and dried in vacuo
15 to afford the title compound (5.8 g, 63%) as a pale yellow powder: ¹H NMR (DMSO-d₆/400 MHz) δ 10.43 (br, 1H), 8.38 (d, 2H, J = 5.2 Hz), 5.77 (d, 1H, J = 2.0 Hz), 5.58 (d, 1H, J = 2.0 Hz), 4.92 (s, 2H), 2.24 (s, 3H), and 2.22 (s, 3H); ESMS m/z 232 (M+H).

20

Step 2



3-Bromo-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

5 The title compound was prepared by a procedure described in step 2 for Example 385.

Yield: 64%, ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 8.47 (s, 1H), 8.42 (s, 1H), 6.07 (s, 1H), 5.38 (s, 2H), 2.51 (s, 3H), and 2.44 (s, 3H), ESMS m/z 310 and 312 ($M+H$).

10

Step 3

To a mixture of 3-Bromo-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (0.45 g, 0.0015 mol), and potassium carbonate (0.25 g, 0.0018 mol) in dimethylacetamide (5.0 mL) was added 2,4 difluorobenzyl bromide (0.25 mL, 0.0019 mol) and stirred at room temperature under argon for 1 h. Dimethylacetamide was distilled in vacuo and the residue was partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The resulting material was purified by flash chromatography (EtOAc/hexane 4:1 v/v) as the eluent. The appropriate fractions (m/z = 451/453) were combined and concentrated under reduced pressure to give a white (0.25 g, 38%) solid. ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 8.49 (s, 1H), 8.40 (s, 1H), 7.60 (m, 1H), 6.99 (m, 2H), 6.51 (s, 1H), 5.42 (s, 2H), 5.29 (s, 2H), 2.54 (s, 3H), and 2.50 (s, 3H); ^{19}F NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ -117.70 (m), and -

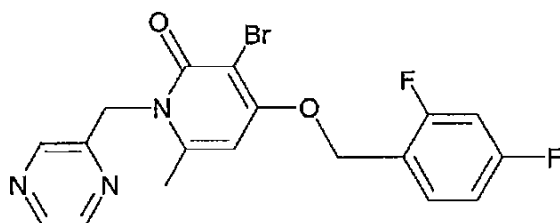
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25

116.09 (m); ES-HRMS m/z 436.0439 ($M+H$ $C_{19}H_{17}N_3O_2BrF_2$ requires 436.0467).

Example 401

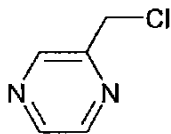
5



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyrazin-2-ylmethyl)pyridin-2(1H)-one

10

Step 1



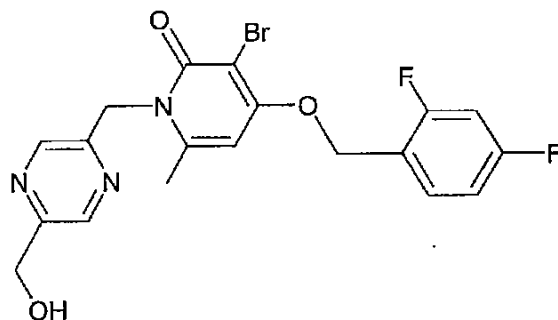
2- Chloromethylpyrazine

15 A mixture of 2-methylpyrazine (3.5 g, 0.037 mol), NCS (6.3 g, 0.047 mol) and benzoyl peroxide (0.05 g) was heated to reflux for 16 h under argon atmosphere. It was filtered and the filtrate was concentrated to dryness. The resulting residue was purified by flash chromatography using 30 % EtOAc in
20 hexane to afford 2-chloromethylpyrazine as a dark colored liquid (1.7 g, 36 %): 1H NMR ($CD_3OD/400$ MHz) δ 8.75 (d, 1H, J = 1.2 Hz), 8.58 (m, 1H), 8.56 (m, 1H), and 4.75 (s, 2H); ESMS m/z = 129 ($M+H$).

25 Step 2

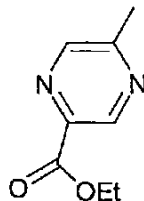
3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one
 (1.8 g, 0.0055 mol) and 2-chloropyrazine (0.8 g, 0.00625)
 were suspended in THF (25 mL), then added NaH (0.15 g, 0.0062
 mol), KI (0.1 g) and the mixture was heated at 65 °C under
 5 argon atmosphere for 16 h. The reaction mixture was cooled,
 added acetic acid (0.5 mL) and concentrated to dryness under
 reduced pressure. The residue was stirred with a mixture of
 water (50 mL) and EtoAc (25 mL) and filtered the precipitate.
 It was washed with water, and acetonitrile and dried in vacuo
 10 to afford 1.7 g of light brown powder. ¹H NMR (CD₃OD/400 MHz)
 δ 8.65 (d, 1H), 8.49 (m, 1H), 8.47 9m, 1H), 7.61 (~ q, 1H), 7.02
 (m, 2H), 6.52 (s, 1H), 5.47 (s, 2H), 5.23 (s, 2H), and 2.53
 (s, 3H);
¹⁹F NMR (CD₃OD/400 MHz) δ -111.72(m), and -116.07 (m); ES-HRMS m/z
 15 422.0283 (M+H C₁₈H₁₅N₃O₂BrF₂ requires 422.0310).

Example 402



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-
 20 (hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

Step 1

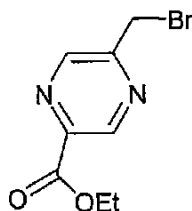


Ethyl 5-methylpyrazine-2-carboxylate

A solution of 5-methylpyrazine-2-carboxylic acid (15.0 g, 0.109 mol) in ethanol (70.0 mL) containing (1.5 g, 0.0079 mol) was heated to reflux for 4 h under argon atmosphere. The dark colored solution was cooled, added sod.bicarbonate (1.0 g) and concentrated under reduced pressure. The residue was partitioned between water (50 mL) and EtOAc (100 mL). The organic layer was washed with water (2 x 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford ethyl 5-methylpyrazine-2-carboxylate (12.05 g, 67%) as an orange colored liquid: ^1H NMR ($\text{CD}_3\text{OD}/400$ MHz) δ 9.1 (d, 1H, $J = 1.2$ Hz), 8.62 (d, 1H, $J = 1.2$ Hz), 4.45 (q, 2H, $J = 7.2$ Hz), 2.63 (s, 3H), and 1.41 (t, 3H, $J = 7.2$ Hz); ESMS m/z 167 ($\text{M}+\text{H}$).

15

Step 2



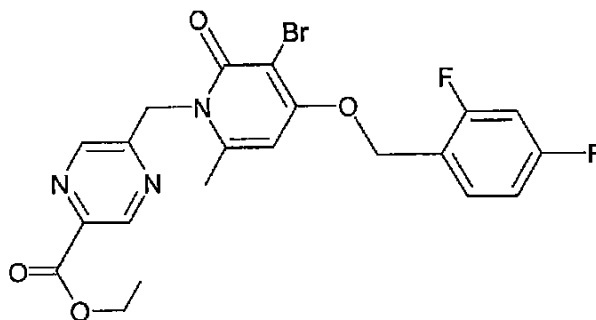
Ethyl 5-(bromomethyl)pyrazine-2-carboxylate

A solution of ethyl 5-methylpyrazine-2-carboxylate (12.0 g, 0.072 mol) in glacial acetic acid (60 mL) containing bromine (4.0 mL) was heated at 80 °C under anhydrous conditions for 45 min. After the removal of acetic acid in vacuo, the residue was partitioned between saturated, bicarbonate (100 mL) and EtOAc (3 x 30 mL). The combined EtOAc extracts were washed with water (2 x 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resulting liquid was purified by flash chromatography (20 %EtOAc in hexane) to afford ethyl-5bromomethylpyrazine-2-carboxylate (7.7 g, 44%) as an orange

colored liquid: ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 9.18 (d, 1H, $J = 1.2\text{ Hz}$), 8.85 (d, 1H, $J = 1.2\text{ Hz}$), 4.71 (d, 2H), 4.47 (q, 2H, $J = 7.2\text{ Hz}$), and 1.42 (t, 3H, $J = 7.2\text{ Hz}$); ES-HRMS m/z 244.9942 ($\text{M}+\text{H}$ $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2\text{Br}$ requires 244.9920).

5

Step 3



10 Ethyl 5-([3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl)pyrazine-2-carboxylate

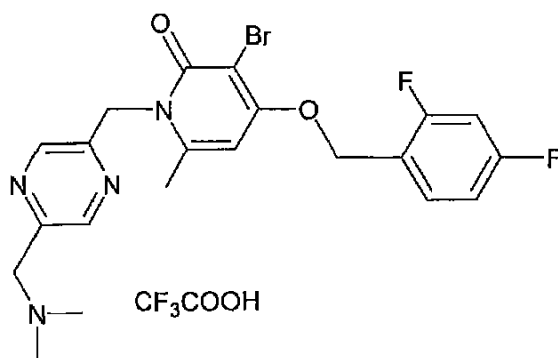
To a mixture of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (6.0 g, 0.018 mol) and ethyl 5-(bromomethyl)pyrazine-2-carboxylate (4.9 g, 0.02 mol) in THF (50.0 mL) was added NaH (0.5 g) and heated at 55 °C under argon atmosphere for 3 h. The reaction mixture was cooled, added acetic acid (1.2 mL) and concentrated under reduced pressure. The residue was triturated with water and filtered the solid. It was washed with water, followed by ethanol and dried in vacuo to afford the title compound (3.0 g, 78%) as a light brown powder: ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 9.10 (d, 1H, $J = 1.2\text{ Hz}$), 8.77 (d, 1H, $J = 1.2\text{ Hz}$), 7.61 (m, 1H), 7.01 (m, 2H), 6.54 (s, 1H), 5.54 (s, 2H), 5.30 (s, 2H), 4.43 (q, 2H, $J = 6.8\text{ Hz}$), 2.52 (s, 3H), and 1.39 (t, 3H, $J = 6.8\text{ Hz}$); ^{19}F NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ -111.64 (m), and -116.04 (m); ES-HRMS m/z 494.0482 ($\text{M}+\text{H}$ $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_4\text{BrF}_2$ requires 494.0522).

25

Step 4

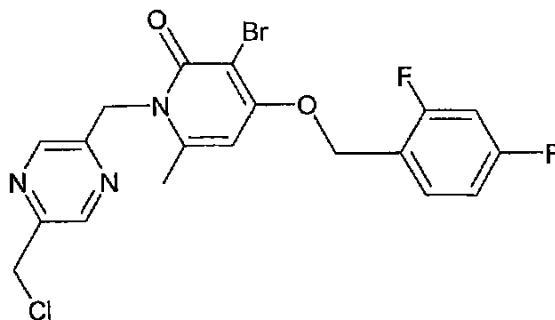
To a suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (2.0 g, 0.004 mol) in t-butanol (15.0 mL) and THF (5.0 mL) was added NaBH₄ (0.18 g, 0.0047 mol) and the mixture was stirred at room temperature for 16 h under argon atmosphere. It was cooled, added MeOH (5.0 mL) and acetic acid (1.0 mL) and concentrated to dryness. The residue was triturated with water and filtered. It was washed with water, dried in vacuo and purified by flash chromatography (1% MeOH in EtOAc to afford the title compound (0.75 g, 41%) as a pale yellow powder: ¹H NMR (CD₃OD/400 MHz) δ 8.58 (d, 1H, J = 1.6 Hz), 8.56 (d, 1H, J = 1.6 Hz), 7.6 (m, 1H), 7.01 (m, 2H), 6.52 (s, 1H), 5.46 (s, 2H), 5.29 (s, 2H), 4.71 (s, 2H), and 2.54 (s, 3H); ¹⁹F NMR (CD₃OD/400 MHz) δ -111.70 (m), and -116.06 (m); ES-HRMS m/z 452.0394 (M+H C₁₉H₁₇N₃O₃BrF₂ requires 452.0416).

Example 403



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-{[(dimethylamino)methyl]pyrazin-2-yl}methyl)-6-methylpyridin-2(1H)-one trifluoroacetate

Step 1



3-Bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

5

Cyanurylchloride (0.42g, 0.0023 mol) was added to DMF (0.52 mL) and stirred at room temperature for 15 min. Then added dichloromethane (15 mL) followed by the addition of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one 1.0 g, 0.0022 mol) and reaction mixture was stirred at room temperature under argon atmosphere. After 1 h, an additional 1.0 mL of DMF was added and the reaction was allowed to proceed for another hour, when a clear solution was obtained. The solution was diluted with dichloromethane (20 mL) and washed with water, dried (Na₂SO₄), and concentrated to dryness under reduced pressure. The residue was triturated with EtOAc, filtered, washed with EtOAc and dried to afford 0.79 g (77%) of the title compound as a pale yellow powder: ¹H NMR (CD₃OD/400MHz) δ 8.66 (s, 2H), 7.73 (m, 1H), 7.05 (m, 2H), 6.56 (s, 1H), 5.52 (s, 2H), 5.33 (s, 2H), 4.74 (s, 2H), and 2.57 (s, 3H); ES-HRMS m/z 470.0051 (M+H C₁₉H₁₆N₃O₂BrClF₂ requires 470.0077).

20

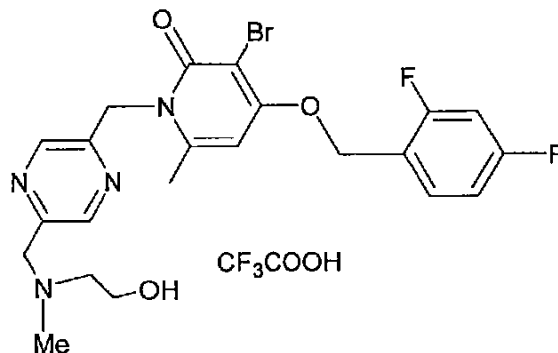
Step 2

25

A suspension of 3-Bromo-1-{[5-(chloromethyl)pyrazin-2-yl]methyl}-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-

one (0.25 g, 0.00053 mol) in THF (1.0 mL) was treated with N, N,-dimethyl amine (1.0 mL of 2M soln in THF) and stirred at room temperature for 16 h. The reaction mixture was concentrated and the title compound was isolated by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 479) were combined and freeze dried to afford the title compound (0.27 g, 87%) as a white powder: ^1H NMR ($\text{CD}_3\text{OD}/400\text{MHz}$) δ 8.78 (d, 1H, J Hz), 8.56 (d, 1H, J = 1.2 Hz), 7.61 (m 1H), 7.01 (m, 2H), 6.55 (s, 1H), 5.49 (s, 2H), 5.30 (s, 2H), 4.52 (s, 2H), 2.94 (s, 6H) and 2.57 (s, 3H); ^{19}F NMR (CD_3OD) = δ -111.56 (m) and -116.02 (m); ES-HRMS m/z 479.0885 (M+H $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2\text{BrF}_2$ requires 479.0889).

15 Example 404



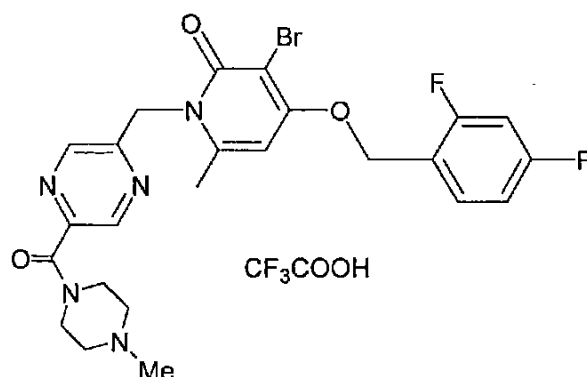
3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-{[(2-hydroxyethyl)(methyl)amino]-methyl}pyrazin-2-yl)methyl]-6-methylpyridin-2(1H)-one trifluoroacetate

The title compound was prepared in a similar manner as described for Example 403, substituting N-methylaminoethanol for N, N-dimethylamine. Yield = 78%,

^1H NMR ($\text{CD}_3\text{OD}/400\text{MHz}$) δ 8.78 (d, 1H, J Hz), 8.59 (d, 1H, J = 1.2 Hz), 7.6 (m, 1H), 7.01 (m, 2H), 6.55 (s, 1H), 5.49 (s,

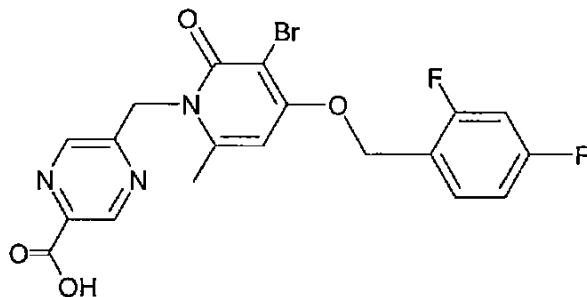
2H), 5.30 (s, 2H), 3.89 (~t, 2H), 2.97 (s, 3H), and 2.57 (s, 3H); ^{19}F NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) = δ -111.56 (m) and -116.04 (m); ES-HRMS m/z 509.0964 ($\text{M}+\text{H}$ $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_3\text{BrF}_2$ requires 509.0994).

5 Example 405



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-
 10 2(1H)-one trifluoroacetate

Step 1



5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid
 15

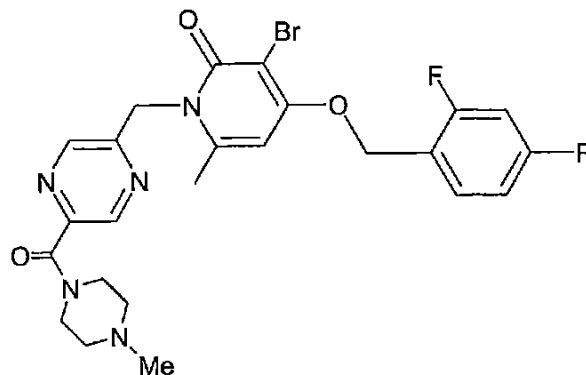
A suspension of ethyl 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylate (0.18 g, 0.002 mol) and 1N NaOH (0.6 mL in 1:1 v/v EtOH/Water) was stirred at room temperature for 1.5 h. The reaction
 20 mixture was acidified with 5% citric acid and filtered the

precipitate. It was washed with water, followed by ethanol and dried in vacuo to afford the title compound (0.14 g, 77%) as a light brown powder: ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) = δ 9.03 (s, 1H), 8.60 (s, 1H), 7.61 (m, 1H), 7.00 (m, 2H), 6.52 (s, 1H), 5.51 (s, 2H), 5.30 (s, 2H), and 2.52 (s, 3H); ^{19}F NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) = δ -111.75 (m) and -116.06 (m); ES-HRMS m/z 466.0209 ($\text{M}+\text{H}$ $\text{C}_{19}\text{H}_{15}\text{N}_4\text{O}_3\text{BrF}_2$ requires 466.0209).

Step 2

To a solution of 5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0.28 g, 0.0006 mol) in DMF (3.0 mL), at $-15\text{ }^\circ\text{C}$, was added isobutylchloroformate (0.082g, 0.0006 mol), followed by the addition of N-methylmorpholine (0.06 g, 0.00063 mol) and stirred under argon for 15 min. N-methylpiperazine (0.072 g, 0.00072 mol) in DMF (2.0 mL) was then added to the reaction and the mixture was stirred at room temperature for 3 h. After the removal of the solvents in vacuo, the residue was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 548) were combined and freeze dried to afford the title compound (0.32 g, 80%) as a white powder: ^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 8.89 (d, 1H, J = 1.6 Hz), 8.73 (d, 1H, J = 1.6 Hz), 7.61 (m, 1H), 7.01 (m, 2H), 6.56 (s, 1H), 5.50 (s, 2H), 5.30 (s, 2H), 2.9 (s, 3H), and 2.57 (s, 3H); ^{19}F NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) = δ - 109.36 (m) and - 114.91 (m); ES-HRMS m/z 548.1090 ($\text{M}+\text{H}$ $\text{C}_{24}\text{H}_{25}\text{N}_5\text{O}_3\text{BrF}_2$ requires 548.1103).

Example 406

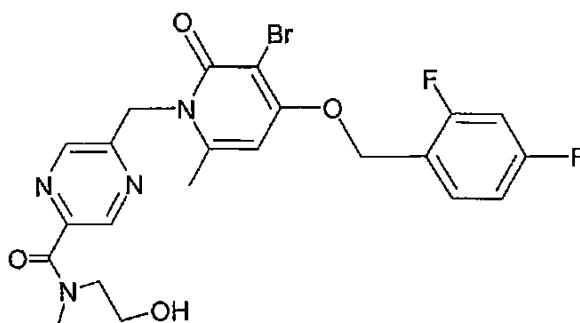


3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one

5

A solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-({5-[(4-methylpiperazin-1-yl)carbonyl]pyrazin-2-yl}methyl)pyridin-2(1H)-one trifluoroacetate (0.17 g, 0.00026 mol) in 0.1N NaOH (25 mL) was stirred at room temperature for 10 15 min. and extracted the product in ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL), dried (Na₂SO₄) and concentrated to dryness. The residue was dried in vacuo to afford the title product (0.09 g, 64%) as a white powder: ¹H NMR (CD₃OD/400 MHz) δ 8.69 (d, 1H, J = 1.2 Hz), 8.67 (d, 1H, J = 1.2 Hz), 7.60 (m, 1H), 7.00 (m, 2H), 6.54 (s, 1H), 5.50 (s, 2H), 5.30 (s, 2H), 3.78 (t, 2H, J = 4.8 Hz), 3.58 (t, 2H, J = 4.8 Hz), 2.526 (s, 3H), 2.53 (t, 2H, J = 4.8 Hz), 2.44 (t, 2H, J = 4.8 Hz), and 2.31 (s, 3H); ¹⁹F NMR (CD₃OD/400 MHz) = δ -111.65 (m) and -116.06 (m); ES-HRMS 20 m/z 548.1123 (M+H C₂₄H₂₅N₅O₃BrF₂ requires 548.1103).

Example 407

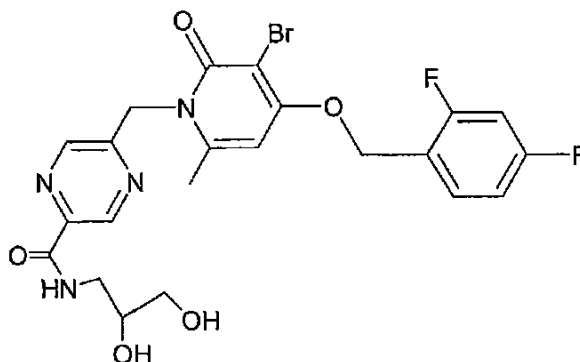


5- { [3-Bromo-4- [(2,4-difluorobenzyl)oxy] -6-methyl-2-
 5 oxopyridin-1(2H) -yl]methyl} -N- (2-hydroxyethyl) -N-
 methylpyrazine-2-carboxamide

The title compound was prepared in a similar manner as
 described for Example 405 , substituting N-methylpiperazine by
 10 N-methylethanolamine. Yield = 60%,

^1H NMR ($\text{CD}_3\text{OD}/400$ MHz) δ 8.69 (d, 1H, $J = 1.2$ Hz), 8.64 (d, 1H,
 $J = 1.2$ Hz), 7.61 (m, 1H), 7.00 (m, 2H), 6.54 (s, 1H), 5.49
 (s, 2H), 5.30 (s, 2H), 3.81 (~ t, 1H), 3.66 (m, 2H), 3.56 (t,
 1H, $J = 5.2$ Hz), 3.12 (d, 3H $J = 7.6$ Hz), 2.56 (s, 3H); ^{19}F NMR
 15 ($\text{CD}_3\text{OD}/400$ MHz) δ -109.64 (m) and -113.66 (m); ES-HRMS m/z 523.0743
 ($M+H$ $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_4\text{BrF}_2$ requires 523.0797).

Example 408



5- { [3-Bromo-4- [(2,4-difluorobenzyl) oxy] -6-methyl-2-oxopyridin-1(2H) -yl]methyl} -N- (2,3-dihydroxypropyl)pyrazine-2-carboxamide

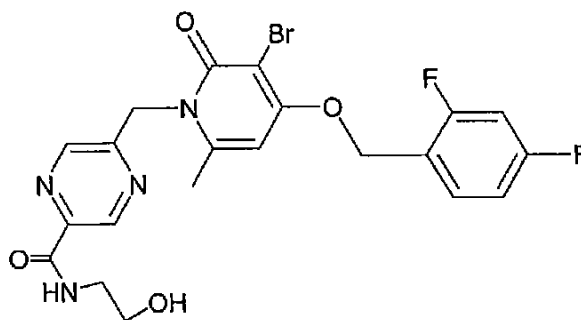
5

The title compound was prepared in a similar manner as described for EXAMPLE 405, substituting N-methylpiperazine by 3-amino-1,2-propanediol. Yield = 56%; ^1H NMR ($\text{CD}_3\text{OD}/400$ MHz) δ 9.09 (d, 1H, $J = 1.2$ Hz), 8.70 (d, 1H, $J = 1.2$ Hz), 7.60 (m, 1H), 7.00 (m, 2H), 6.54 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 3.80 (m, 1H), 3.61 (dd, 1H), 5.53 (d, 2H), $J = 5.2$ Hz), 3.42 (dd, 1H), and 2.55 (s, 3H); ^{19}F NMR ($\text{CD}_3\text{OD}/400$ MHz) δ -109.65 (m), and -113.67 (m); ES-HRMS m/z 539.0703 ($\text{M}+\text{H}$ $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_4\text{BrF}_2$ requires 539.0736).

10

15

Example 409



20 5- { [3-Bromo-4- [(2,4-difluorobenzyl) oxy] -6-methyl-2-oxopyridin-1(2H) -yl]methyl} -N- (2-hydroxyethyl)pyrazine-2-carboxamide

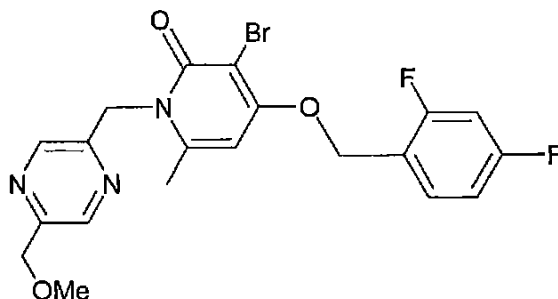
25

The title compound was prepared in a similar manner as described for EXAMPLE 405, substituting N-methylpiperazine by 2-aminoethanol. Yield = 46%; ^1H NMR ($\text{CD}_3\text{OD}/400$ Hz) δ 9.08 (d, 1H, $J = 1.2$ Hz), 8.70 (d, 1H, $J = 1.2$ Hz), 7.601 (m, 1H), 7.01 (m, 2H), 6.54 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 3.69 (t, 2H, $J = 6.0$ Hz), 3.53 (t, 2H, $J = 6.0$ Hz), 2.55 (s, 3H); ^{19}F

NMR (CD₃OD/400 Hz) δ -111.67 (m) and -116.07 (m); ES-HRMS m/z 509.0616 (M+H C₂₁H₂₀N₄O₄BrF₂ requires 509.0630).

Example 410

5



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-

10 (methoxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one

To a solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0.35 g, 0.00078 mol) in DMF at 0 °C, was added NaH (0.022 g,

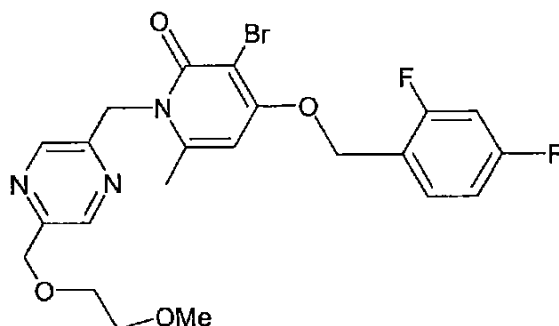
15 0.00092 mol) and stirred for 10 min. Iodomethane (0.05 mL) was added to the reaction and the mixture was stirred at 10 °C for 3 h. DMF was distilled in vacuo and the residue was partitioned between 5% citric acid and EtOAc (15.0 mL). The organic phase was washed with water, dried (Na₂SO₄) and

20 concentrated to dryness. The residue was purified by flash chromatography (EtOAc), and the appropriate fractions were combined and concentrated to a pale yellow powder.

¹H NMR (CD₃OD/400 MHz) δ 8.59 (s), 8.55 (s, 1H), 7.60 (m, 1H), 6.99 (m, 2H), 6.52 (s, 1H), 5.47 (s, 2H), 5.30 (s, 2H), 4.57 (s, 2H), 3.44 (s, 2H), and 2.54 (s, 3H); ¹⁹F NMR (CD₃OD/400 Hz)

25 δ -111.69 (m) and -116.09 (m); ES-HRMS m/z 466.0577 (M+H C₂₁H₁₉N₃O₃BrF₂ requires 466.0572).

Example 411

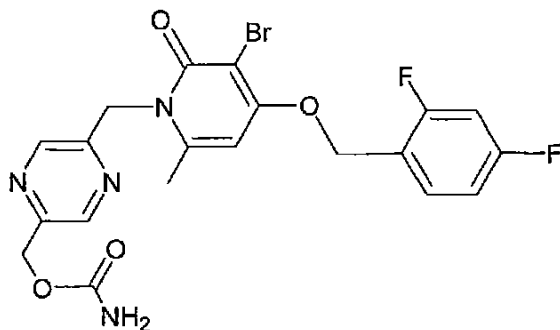


5 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-[(2-methoxyethoxy)methyl]pyrazin-2-yl)methyl]-6-methylpyridin-2(1H)-one

To a solution of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-(hydroxymethyl)pyrazin-2-yl)methyl]-6-methylpyridin-2(1H)-one (0.25 g, 0.00055 mol) in dimethyl acetamide at
 10 0 °C, was added NaH (0.016 g, 0.00067 mol) and stirred for 15 min. 2-Methoxyethyl bromide (0.09 g, 0.00065 mol) was then added, and the mixture was stirred at room temperature for 6
 15 h. Dimethylacetamide was distilled in vacuo and the product was purified by reverse-phase HPLC using 10 - 90% acetonitrile/water gradient (30 min) at a flow rate of 100 mL/min. The appropriate fractions (m/z = 510) were combined and freeze dried to afford the title compound (0.32 g, 80%) as
 20 a white powder:

^1H NMR ($\text{CD}_3\text{OD}/400\text{ Hz}$) δ 8.59 (s, 1H), 8.58 (s, 1H), 7.60 (m, 1H), 7.02 (m, 2H), 6.52 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 4.67 (s, 2H), 3.71 (~t, 2H,), 3.57 (~t, 2H), 3.34 (s, 3H), and 2.54 (s, 3H); ES-HRMS m/z 510.0852 ($\text{M}+\text{H}$ $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{BrF}_2$ requires
 25 510.0835).

Example 412



(5-{[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazin-2-yl)methyl carbamate

5

To a suspension of 3-Bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyrazin-2-yl]methyl}-6-methylpyridin-2(1H)-one (0.21 g, 0.00055 mol) in THF (5.0 mL) and DMF (2.0 mL), was added 4-nitrophenylchloroformate (0.1 g, 0.0005 mol) and

10 cooled to 0 °C. Triethylamine (0.052g, 0.0005 mol) was then added, stirred at room temperature for 1 h, and at 65 °C for an additional 1h. It was cooled in an ice bath and added 2M ammonia in propanol (1.0 mL) and stirred at room temperature for 2 h. After the removal of the solvents under reduced

15 pressure, the residue was partitioned between 5% sod.

bicarbonate, and EtOAc (25 mL). The organic phase was washed with 5% sod. bicarbonate, (3 x 25 mL), water (3 x 25 mL),

dried (Na₂SO₄) and concentrated under reduced pressure. The resulting substance was purified by isolated by reverse-phase

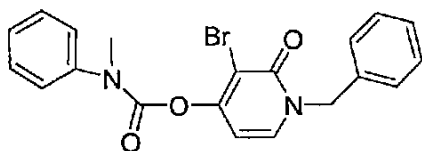
20 HPLC using 10 -90% CH₃CN/Water (30 min gradient) at a flow rate of 100 mL/min. The appropriate fractions (m/z= 495 M+H) were combined and freeze-dried, and the residue was partitioned

between 5% sod. bicarbonate (20 mL) and EtOAc (25 mL). The organic phase was washed with water, dried (Na₂SO₄) and

25 concentrated to dryness under reduced pressure, to afford the title compound as a white powder (0.065 g):

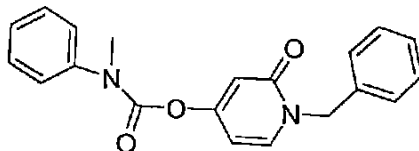
^1H NMR ($\text{CD}_3\text{OD}/400\text{ MHz}$) δ 8.61 (br s, 1H), 8.54 (br s, 1H), 7.60 (m 1H), 7.02 (m, 2H), 6.52 (s, 1H), 5.47 (s, 2H), 5.29 (s, 2H), 5.15 (s, 2H), and 2.54 (s, 3H): ^{19}F NMR (CD_3OD) δ -111.70 (m), and -116.09 (m); ES-HRMS m/z 495.0449 ($\text{M}+\text{H}$ $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_4\text{BrF}_2$ requires 495.0474).

Example 413



1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl
methyl (phenyl) carbamate

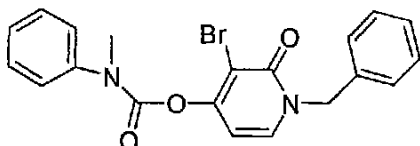
Step 1. Preparation of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl
methyl (phenyl) carbamate



To a chilled solution of 1-benzyl-4-hydroxypyridin-2(1H)-one (0.375 g, 1.86 mmol) in anhydrous acetonitrile (10 mL) was added triethylamine (0.206 g, 2.04 mmol) followed by N-methyl-N-phenylcarbamoyl chloride (0.379 g, 2.24 mmol). The reaction mixture was stirred under nitrogen atmosphere at 0°C for 30 minutes then at room temperature for 1 hour. The reaction was monitored by TLC (5% methanol in dichloromethane). The solvent was removed under reduced pressure and the residue was washed with 10% citric acid and extracted with ethyl acetate. The organic extracts were combined, washed with water and dried over anhydrous Na_2SO_4 . The solvent was removed under

reduced pressure to afford a yellow syrup. The residue was purified by flash chromatography (silica gel) using 5% MeOH in CH_2Cl_2 to give the desired product (0.382g, 61%) as a white semisolid. $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ 7.8 (d, 1H, J = 7.2 Hz), 7.39 (m, 10H), 6.19 (s, 2H), 5.03 (s, 2H), 3.29 (s, 3H); ES-HRMS m/z 335.1396 ($M+H$ calculated for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3$ requires 335.1418).

Step 2. Preparation of 1-benzyl-3-bromo-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate

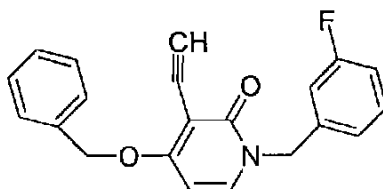


To a solution of 1-benzyl-2-oxo-1,2-dihydropyridin-4-yl methyl(phenyl)carbamate (0.38 g, 1.13 mmol) in anhydrous CH_2Cl_2 (7 mL) was added N-Bromosuccinimide (NBS, 0.24 g, 1.34 mmol). The reaction was stirred overnight at room temperature under nitrogen atmosphere. The reaction mixture was purified by flash chromatography (silica gel) using ethyl acetate/hexane (1:1 v/v). The appropriate fractions were collected according to ES MS ($M+H$ 413) and concentrated. The dried product showed about 14% of di-bromonated product by analytical HPLC. The compounds were separated by reverse phase HPLC using a 10-90% acetonitrile in water (30 minute gradient) at a 100 mL/min flow rate to afford (after lyophilization) the salt of the desired compound. The salt was diluted in ethyl acetate and washed with NaHCO_3 . The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to afford the desired compound (0.271 g, 58%) as a beige solid. $^1\text{H-NMR}$ (d_6 -DMSO, 400 MHz) δ 7.94 (d, 1H, J = 7.2 Hz), 7.29 (m, 10H), 6.48 (s, 1H),

5.12 (s, 2H), 3.33 (s, 3H); ES-HRMS m/z 413.0495 (M+H calculated for C₂₀H₁₆O₃Br requires 413.0496).

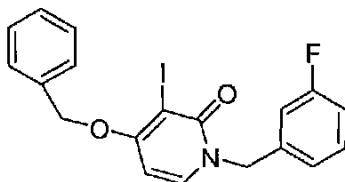
Example 414

5



4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one

10 Step 1. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one

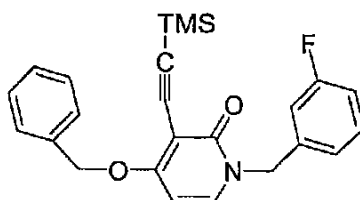


A mixture of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-
15 2(1H)-one (4.83 g, 15.6 mmol) in anhydrous acetonitrile (55 mL) and N-iodosuccinimide (NIS, 3.86 g, 17.1 mmol) was heated at 65° C under nitrogen for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel) using ethyl
20 acetate/hexane (1:1 v:v). The appropriate fractions were collected according to ES MS (M+H 436) and washed with Na₂SO₃ to remove the color impurities. The fractions were concentrated under reduced pressure and dried in vacuo to afford the desired product (6.15 g, 90%) as a light yellow
25 solid. ¹H-NMR (CD₃OD, 400 MHz) δ7.73 (d, 1H, J= 7.6 Hz), 7.47 (d, 2H, J= 7.2 Hz), 7.39 (m, 4H), 7.08 (m, 3H), 6.39 (d, 1H,

J= 8.0 Hz), 5.29 (s, 2H), 5.19 (s, 2H); ES-HRMS m/z 436.0210 (M+H calculated for C₁₉H₁₆NO₂FI requires 436.0196).

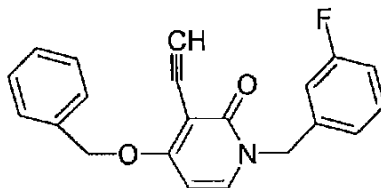
Step 2. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-

5 [(trimethylsilyl)ethynyl]pyridin-2(1H)-one



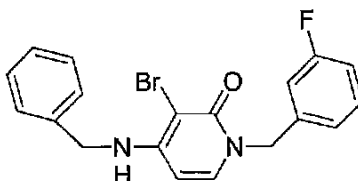
Degassed a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one (2.01 g, 4.62 mmol) in anhydrous
10 acetonitrile (25 mL) under argon atmosphere. Triethylamine (1.11 g, 11 mmol) was added and quickly degassed. The reaction mixture was chilled in an ice bath for 15 minutes before adding bistriphenylphosphine-palladium chloride (0.34 g, 0.48 mmol) and cuprous iodide (0.2 g). The reaction was
15 stirred at room temperature for 30 minutes before heating at 60° C under an atmosphere of argon for 2 hours. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure. The dark brown residue was diluted with CH₂Cl₂ (100 mL) and washed with water.
20 The organic extracts were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The dark brown residue was purified by flash chromatography using 30% ethyl acetate in hexane. The appropriate fractions were combined and concentrated under reduced pressure to afford the
25 desired product (1.34 g, 72%) as a light yellow solid. ¹H-NMR (CD₃OD, 400 MHz) δ7.74 (d, 1H, J= 7.6 Hz), 7.47 (d, 2H, J= 7.6 Hz), 7.35 (m, 4H), 7.09 (m, 3H), 6.46 (d, 1H, J= 7.6 Hz), 5.26 (s, 2H), 5.13 (s, 2H), 0.18 (s, 9H); ES-HRMS m/z 406.1638 (M+H calculated for C₂₄H₂₅NO₂FSi requires 406.1610).

Step 3. Preparation of 4-(benzyloxy)-3-ethynyl-1-(3-fluorobenzyl)pyridin-2(1H)-one



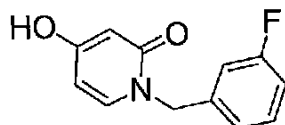
5 To a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-[(trimethylsilyl)ethynyl]pyridin-2(1H)-one (1.31 g, 3.2 mmol) in anhydrous acetonitrile (25 mL) at 0° C was added tetrabutylammonium fluoride (0.611g, 1.93 mmol). The reaction was stirred at 0° C for 15 minutes then for 1 hour at room
10 temperature. The reaction was concentrated under reduced pressure and the residue was diluted with ethyl acetate and washed with water. The organic extracts were combined, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel) using ethyl acetate in hexane (1:1 v/v). The appropriate
15 fractions were combined and concentrated under reduced pressure to afford the desired product (0.779 g, 72%) as a gold solid. ¹H-NMR (CD₃OD, 400 MHz) δ7.73 (d, 1H, J= 7.6 Hz), 7.43 (d, 2H, J= 7.2 Hz), 7.35 (m, 4H), 7.09 (m, 3H), 6.45 (d, 1H, J= 7.6 Hz), 5.27 (s, 2H), 5.13 (s, 2H), 3.78 (s, 1H); ES-
20 HRMS m/z 334.1243 (M+H calculated for C₂₁H₁₇NO₂F requires 334.1234).

Example 415



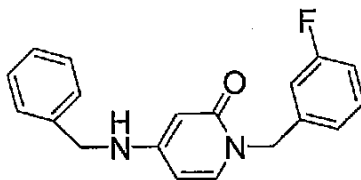
4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one

- 5 Step 1. Preparation of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one



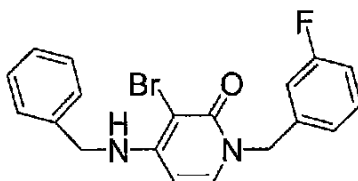
- In a Fischer-Porter bottle, added a solution of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4.5 g, 14.56 mmol) in absolute ethanol (20 mL). Flushed the solution with nitrogen then added palladium catalyst (1.05 g, 10% Pd/C). Sealed bottle and evacuated system. The system was purged with hydrogen gas (2 X 15 psi) to check for leaks. The reaction was charged with hydrogen (35 psi) and stirred at room temperature for 45 minutes. The system was evacuated and flushed with nitrogen. The reaction was filtered and the catalyst was carefully washed with fresh ethanol. The filtrate was concentrated under reduced pressure. ¹H-NMR (CD₃OD, 400 MHz) δ7.54 (d, 1H, J= 7.6 Hz), 7.32 (m, 1H), 7.06 (d, 1H, J= 7.6 Hz), 6.99 (m, 2H), 6.05 (dd, 1H, J= 2.4 Hz, 2.8 Hz), 5.83 (d, 1H, J= 2.4 Hz), 5.09 (s, 2H); ES-HRMS m/z 220.0774 (M+H calculated for C₁₂H₁₁NO₂F requires 220.0787).

- 25 Step 2. Preparation of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one



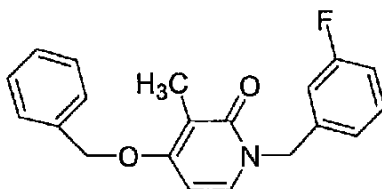
A mixture of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (1.005 g, 4.5 mmol) in benzylamine (15 mL) was heated at reflux (185° C) under nitrogen atmosphere for 24 hours. The reaction was monitored by ES-MS (MH⁺ 309). The solvent was removed by vacuum distillation to give a yellow residue. ¹H-NMR (CD₃OD, 400 MHz) δ7.31 (m, 7H), 7.03 (m, 3H), 5.98 (d, 1H, J= 7.2 Hz), 5.45 (s, 1H), 5.00 (s, 2H), 4.30 (s, 2H); ES-HRMS m/z 309.1403 (M+H calculated for C₁₉H₁₈N₂OF requires 309.1375).

Step 3. Preparation of 4-(benzylamino)-3-bromo-1-(3-fluorobenzyl)pyridin-2(1H)-one



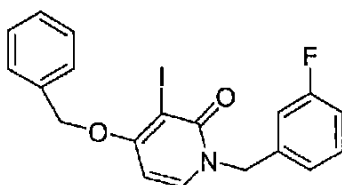
To a solution of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one (0.50 g, 1.62 mmol) in anhydrous CH₂Cl₂ (10 mL) was added N-bromosuccinimide (NBS, 0.30 g, 1.7 mmol). The reaction was stirred at room temperature under a nitrogen atmosphere for 3 hours. The reaction mixture was purified by flash chromatography (silica gel) using ethyl acetate in hexane (1:1 v/v). The appropriate fractions were combined and concentrated. ¹H-NMR (CD₃OD, 400 MHz) δ7.41 (d, 1H, J= 7.6 Hz), 7.31 (m, 6H), 7.04 (m, 3H), 5.99 (d, 1H, J= 7.6 Hz), 5.08 (s, 2H), 4.53 (s, 2H); ES-HRMS m/z 387.0508 (M+H calculated for C₁₉H₁₇N₂OBrF requires 387.0504).

Example 416



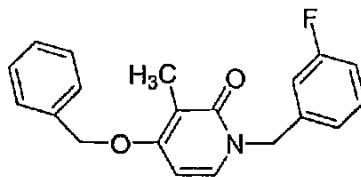
4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1H)-one

5 Step 1. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one



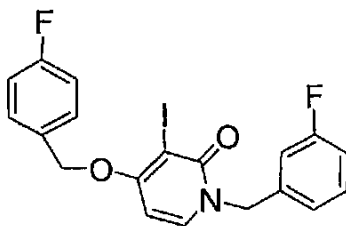
A mixture of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one (4.83 g, 15.6 mmol) and N-iodosuccinimide (NIS, 3.86 g, 17.1 mmol) in anhydrous acetonitrile (55 mL) was heated at 65° C for 4 hours under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate/hexane 1:1 v/v). The appropriate fractions were collected according to ES MS ($M+H$ 436) and washed with Na_2SO_3 to remove the color impurities. The fractions were concentrated under reduced pressure and dried in vacuo to afford the desired product (6.15 g, 90%) as a light yellow solid. 1H -NMR (CD_3OD , 400 MHz) δ 7.73 (d, 1H, J = 7.6 Hz), 7.36 (m, 6H), 7.08 (m, 3H), 6.39 (d, 1H, J = 8.0 Hz), 5.28 (s, 2H), 5.19 (s, 2H); ES-HRMS m/z 436.0196 ($M+H$ calculated for $C_{19}H_{16}NO_2FI$ requires 436.0210).

Step 2. Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-methylpyridin-2(1H)-one



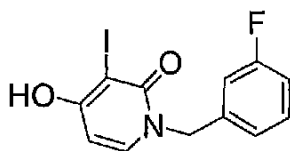
To a degassed solution of 4-(benzyloxy)-1-(3-fluorobenzyl)-3-iodopyridin-2(1H)-one (1.03 g, 2.36 mmol) in anhydrous DMF (15 mL) under argon atmosphere was added
5 triethylamine (1.11 g, 11 mmol). The reaction mixture was chilled in an ice bath for 15 minutes before adding tetramethyl tin (2.10 g, 11.75 mmol) followed by bistriphenylphosphine-palladium chloride (0.166 g, 0.24 mmol). The reaction was stirred at room temperature for 30 minutes
10 before heating at 95° C under an atmosphere of argon for 3 hours. The reaction mixture was filtered through a bed of celite and the filtrate was concentrated under reduced pressure. The dark brown residue was diluted with ethyl acetate (100 mL) and washed with water. The organic extracts
15 were combined, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The dark brown residue was purified by flash chromatography (30% ethyl acetate in hexane). The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0.1758 g, 22%)
20 as a light yellow solid. The product was further purified by reverse phase HPLC using a 10-90% acetonitrile/water (30 minute gradient) at a 100 mL/min flow rate, to afford a cleaner product as a light yellow solid (0.0975g, 8%). ¹H-NMR (CD₃OD, 400 MHz) δ7.58 (d, 1H, J= 7.6 Hz), 7.35 (m, 6H), 6.98 (m, 3H), 6.46 (d, 1H, J= 7.6 Hz), 5.19 (s, 2H), 5.15 (s, 2H),
25 2.0 (s, 3H); ES-HRMS m/z 324.1366 (M+H calculated for C₂₀H₁₉NO₂F requires 324.1394).

Example 417



1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-
2(1H)-one

Step 1: Preparation of 1-(3-fluorobenzyl)-4-hydroxy-3-iodopyridin-2(1H)-one



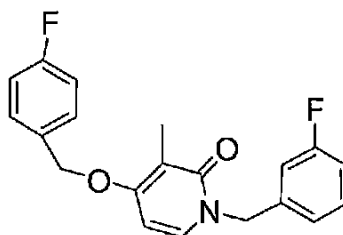
To a mixture of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one (1.1 g, 5 mmol) in acetonitrile (15 mL) was added N-iodosuccinimide (1.1 g, 5.5 mmol) along with a ca. amount of dichloroacetic acid (0.1 mL). The reaction mixture stirred at room temperature for 1 hour under nitrogen. The mixture was chilled in an ice bath and filtered cold with fresh MeCl_2 . The beige solid was dried to afford the desired iodinated intermediate (1.21g, 69%). ES-LRMS m/z 346.

Step 2: Preparation of 1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one

To a mixture of 1-(3-fluorobenzyl)-4-hydroxy-3-iodopyridin-2(1H)-one (0.5g, 1.44 mmol) in DMF (5 mL) was added K_2CO_3 (0.199g, 1.44 mmol) followed by the addition of 4-fluorobenzyl bromide (0.189 mL, 1.51 mmol). The reaction

mixture stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate (50 mL) and washed with water. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. ^1H -NMR (CD_3OD , 400 MHz) δ 7.75 (d, 1H, $J = 7.6$ Hz), 7.49 (q, 2H), 7.34 (q, 1H), 7.11 (m, 5H), 6.40 (d, 1H, $J = 7.6$ Hz), 5.26 (s, 2H), 5.19 (s, 2H); ES-HRMS m/z 454.0098 ($M+H$ calculated for $\text{C}_{19}\text{H}_{15}\text{NO}_2\text{F}_2\text{I}$ requires 454.0110).

Example 418



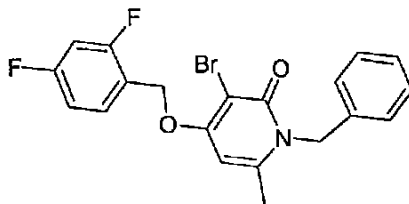
1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-methylpyridin-2(1H)-one

To a degassed solution of 1-(3-fluorobenzyl)-4-[(4-fluorobenzyl)oxy]-3-iodopyridin-2(1H)-one (0.804g, 1.7 mmol) in DMF (10 mL) and LiCl (0.25g, 5.9 mmol) was added tetramethyltin (0.49 mL, 3.54 mmol) followed by bistriphenylphosphine-palladium chloride catalyst (0.124g, 0.177 mmol). The reaction mixture was heated in an oil bath (85°-90° C) under nitrogen for 3 hours. The solvent was concentrated and the residue was diluted with ethyl acetate and washed with water. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified by flash column chromatography (20% ethyl acetate in hexane). The appropriate fractions were concentrated. ^1H -NMR (CD_3OD , 400 MHz) δ 7.59 (d, 1H, $J = 7.6$ Hz), 7.46 (m, 2H), 7.34 (m, 1H), 7.10 (m, 4H), 6.46 (d, 1H, $J = 7.6$ Hz), 5.17 (s, 2H),

5.15 (s, 2H), 1.99 (s, 3H); ES-HRMS m/z 342.1314 (M+H calculated for C₂₀H₁₈NO₂F₂ requires 342.1300).

Example 419

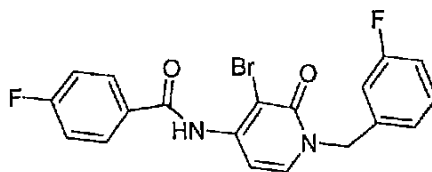
5



1-benzyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-
2(1H)-one

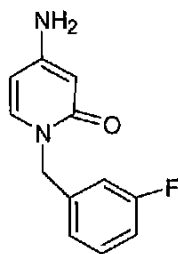
10 To a degassed cold solution of DMF (10 mL) and PPh₃
(resin, 0.93 g, 2.75 mmol) was added DEAD (0.44 mL, 2.75
mmol). The reaction mixture stirred at -10°C for 20 minutes
under nitrogen. A solution of 1-benzyl-3-bromo-4-hydroxy-6-
methylpyridin-2(1H)-one (0.62 g, 2.1 mmol) and 2,4-
15 difluorobenzylalcohol (0.283 mL, 2.5 mmol) in DMF (10 mL) was
added to the resin suspension. The reaction mixture stirred
at -10° C for 30 minutes and then allowed to stir at room
temperature for 1 hour. The resin was filtered and rinsed
with fresh MeOH and the filtrate was concentrated. The residue
20 was dissolved in ethyl acetate and purified by flash column
chromatography (ethyl acetate/hexane 1:1 v/v). The
appropriate fractions were concentrated. ¹H-NMR (CD₃OD, 400
MHz) δ 7.62 (m, 1H), 7.31 (m, 3H), 7.1 (d, 2H, J= 7.2 Hz), 7.02
(t, 2H, J= 8.6 Hz), 6.48 (s, 1H), 5.42 (s, 2H), 5.28 (s, 2H),
25 2.34 (s, 3H); ES-HRMS m/z 420.0399/422.0380 (M+H calculated
for C₂₀H₁₇NO₂F₂Br requires 420.0405/422.0387).

Example 420



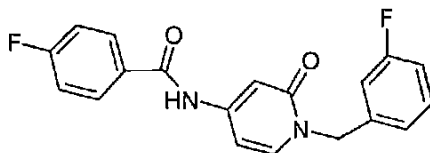
N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-
4-fluorobenzamide

Step 1. Preparation of 4-amino-1-(3-fluorobenzyl)pyridin-
2(1H)-one



In a Fischer-Porter bottle, added a solution of 4-(benzylamino)-1-(3-fluorobenzyl)pyridin-2(1H)-one (2.5g, 8.11 mmol) in glacial acetic acid (20 mL). After the solution was flushed with nitrogen, catalyst was added (10%Pd/C, 2.0g). The vessel was sealed, evacuated, and purged with hydrogen gas. The system was charged with hydrogen gas (50psi) and the mixture stirred at room temperature for 4 hours. The system was evacuated and flushed with nitrogen. The reaction mixture was filtered through a bed of celite and washed with fresh ethanol. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate 3:4 v/v). The filtrate was concentrated. ¹H-NMR (CD₃OD, 400 MHz) δ 7.32 (q, 1H), 7.02 (m, 3H), 5.93 (dd, 1H, J= 2.4 Hz, 2.8 Hz), 5.58 (d, 1H, J= 2.4 Hz); ES-HRMS m/z 219.0966 (M+H calculated for C₁₂H₁₂N₂OF requires 219.0928).

Step 2. Preparation of 4-fluoro-N-[1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzamide



5 To a solution of 4-amino-1-(3-fluorobenzyl)pyridin-2(1H)-one (0.263 g, 1.2 mmol) in acetonitrile (7 mL) was added a DMAP (ca.), triethylamine (0.25 mL, 1.8 mmol) and 4-fluorobenzoyl chloride (0.213 mL, 1.8 mmol). The reaction mixture stirred at 0° C for 25 minutes and then filtered. The
10 solid was washed with 10% citric acid and water to afford the desired compound (0.326 g, 79%) after drying. ¹H-NMR (d₆DMSO, 400 MHz) δ 7.98 (m, 2H), 7.71 (d, 1H, J= 7.6 Hz), 7.35 (m, 3H), 7.08 (m, 3H), 6.98 (d, 1H, J= 2.4 Hz), 6.61 (dd, 1H, J= 2.4 Hz, 2.4 Hz), 5.03 (s, 2H); ESI/MS m/z 341.1.

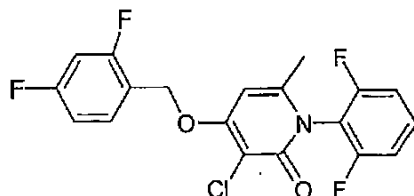
15

Step3. Preparation of N-[3-bromo-1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]-4-fluorobenzamide

To a mixture of 4-fluoro-N-[1-(3-fluorobenzyl)-2-oxo-1,2-dihydropyridin-4-yl]benzamide (0.305g, 0.89 mmol) in
20 acetonitrile (7 mL) was added NBS (0.159g, 0.89 mmol). The reaction mixture stirred at room temperature for 1.5 hours. The filtrate was removed under reduced pressure and the residue was purified by flash column chromatography (ethyl
25 acetate/hexane 1:1 v/v). The fractions were concentrated. ¹H-NMR (CD₃OD, 400 MHz) δ 8.03 (m, 2H), 7.79 (d, 1H, J= 7.6 Hz), 7.47 (d, 1H, J= 8.0 Hz), 7.28 (m, 3H), 7.12 (m, 3H), 5.23 (s, 2H); ES-HRMS m/z 419.0202/421.0191 (M+H calculated for C₁₉H₁₄N₂O₂F₂Br requires 419.0201/421.0183).

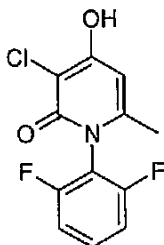
30

Example 421



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-
methylpyridin-2(1H)-one

Step 1. Preparation of 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



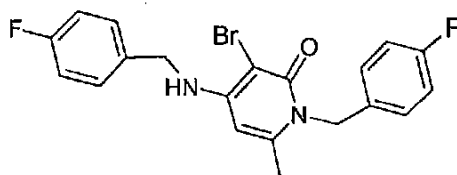
To a mixture of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.30 g, 1.26 mmol) in dichloromethane (5 mL) was added NCS (2.52 g, 1.90 mmol). The reaction mixture stirred at room temperature under nitrogen for 4.5 hours. The suspension was cooled in ice bath, filtered, and the solid was rinsed with fresh dichloromethane to afford the desired product (0.271 g, 79%) as a white solid. ¹H-NMR (CD₃OD, 400 MHz) δ 7.58 (m, 1H), 7.22 (m, 2H), 6.20 (s, 1H), 2.00 (s, 3H); ES-HRMS m/z 272.0287 (M+H calculated for C₁₂H₉NO₂F₂Cl requires 272.0290).

Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

To a solution of 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.27 g, 1.00 mmol) in DMA

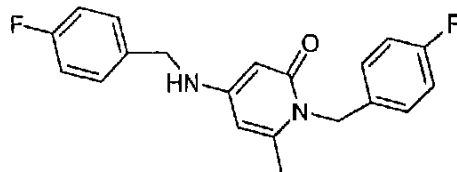
(5 mL) was added K_2CO_3 followed by the addition of 2,4-difluorobenzyl bromide (0.128 mL, 1 mmol). The reaction mixture stirred at room temperature for 2 hours and then was diluted in water. The reaction mixture was extracted with ethyl acetate, the organic extracts were dried over Na_2SO_4 and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (ethyl acetate/hexane 3:4 v/v) to afford the desired product. 1H -NMR (CD_3OD , 400 MHz) δ 7.60 (m, 2H), 7.25 (m, 2H), 7.04 (m, 2H), 6.71 (s, 1H), 5.36 (s, 2H), 2.11 (s, 3H); ES-HRMS m/z 398.0551 ($M+H$ calculated for $C_{19}H_{13}NO_2F_4Cl$ requires 398.0571).

Example 422



3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one



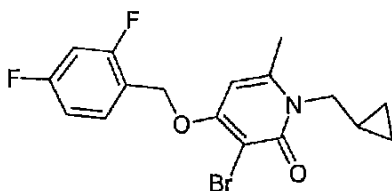
A mixture of 4-hydroxy-6-methylpyrone (5.0 g, 0.04 mol) and 4-fluorobenzylamine (10.0 g, 0.08 mol) in n-butanol (25.0 mL) was heated to reflux for 24 hours under argon atmosphere. The resulting solution was concentrated to dryness under reduced pressure. The residue was triturated with ethyl acetate and filtered. It was thoroughly washed with ethyl

acetate and dried to afford the title compound as a pale yellow powder (4.1 g, 30%). $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ 7.33 (q, 2H), 7.04 (m, 5H), 5.85 (d, 1H, $J = 2.0$ Hz), 5.44 (d, 2H, $J = 2.4$ Hz), 5.20 (s, 1H), 4.29 (s, 2H), 2.17 (s, 3H); ES-HRMS m/z 341.1488 ($M+H$ calculated for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{OF}_2$ requires 341.1460).

Step 2: Preparation of 3-bromo-1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one

To a solution of 1-(4-fluorobenzyl)-4-[(4-fluorobenzyl)amino]-6-methylpyridin-2(1H)-one (0.2857 g, 0.84 mmol) in MeCl_2 was added NBS (0.156 g, 0.88 mmol). The reaction stirred at room temperature under nitrogen for 45 minutes. The reaction mixture was diluted with MeCl_2 and washed with NaHCO_3 . The organic extracts were washed with water, dried over Na_2SO_4 , and concentrated to afford the desired product (0.3242 g, 92%) as a yellow solid. $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ 7.32 (q, 2H), 7.04 (m, 6H), 5.91 (s, 1H), 5.28 (s, 2H), 4.50 (s, 2H), 2.17 (s, 3H); ES-HRMS m/z 419.0549/421.0537 ($M+H$ calculated for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{OBrF}_2$ requires 419.0565/421.0547).

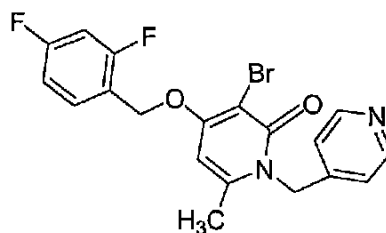
Example 423



3-bromo-1-(cyclopropylmethyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

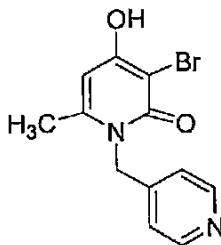
To a mixture of 3-bromo-1-(cyclopropylmethyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.276 g, 1.07 mmol) and K_2CO_3 (0.148 g, 1.07 mmol) in DMA (4 mL) was added 2, 4-difluorobenzyl bromide (0.14 mL, 1.07 mmol). The mixture stirred at room temperature for 1.5 hours. The reaction mixture was diluted in water and extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:1 v/v). The appropriate fractions were combined, and concentrated. 1H -NMR (CD_3OD , 400 MHz) δ 7.60 (q, 1H), 7.04 (m, 2H), 6.42 (s, 1H), 5.26 (s, 2H), 4.06 (s, 1H), 4.04 (s, 1H), 2.50 (s, 3H), 0.53 (m, 2H), 0.43 (m, 2H); ES-HRMS m/z 384.0392 ($M+H$ calculated for $C_{17}H_{17}N_2OBrF_2$ requires 384.0405).

Example 424



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one

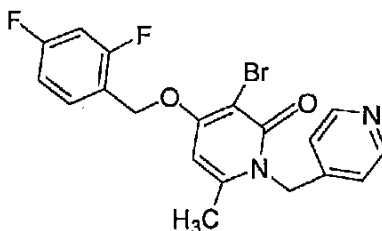
Step 1. Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



Commercially available 4-hydroxy-6-methyl pyrone (10 g, 79.3 mmol) was condensed with commercially available 4-(aminomethyl) pyridine (8 mL, 79.3 mmol) in water (50mL). The mixture was heated in an oil bath at reflux for 1 hour under nitrogen. The solvent was evaporated. MS and ¹H-NMR were consistent with the desired desbrominated structure. ¹H-NMR (CD₃OD, 400 MHz) δ 8.45 (dd, 2H, J= 1.6 Hz, 1.6 Hz), 7.15 (d, 2H, J= 6.0 Hz), 6.00 (d, 1H, J= 2.0 Hz), 5.80 (d, 1H, J= 2.4 Hz), 5.34 (s, 2H), 2.23 (s, 3H); ES-LRMS (M+H) m/z 217.

To a suspension of the above compound (0.801 g, 3.7 mmol) in MeCl₂ (10 mL) was added NBS (0.725 g, 4.07 mmol). The reaction mixture stirred at room temperature for 30 minutes under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh MeCl₂ and dried to afford a beige solid (0.9663 g, 88%) after drying. ¹H-NMR (CD₃OD, 400 MHz) δ 8.47 (d, 2H, J= 5.2 Hz), 7.16 (d, 2H, J= 6.0 Hz), 6.09 (s, 1H), 5.40 (s, 2H), 2.24 (s, 3H); ES-LRMS (M+H) m/z 295/297.

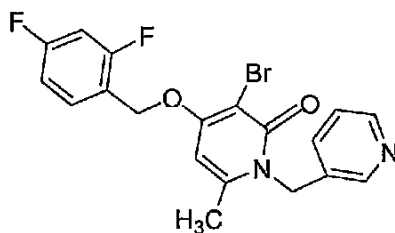
Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



To a cold solution of 2,4-difluorobenzylalcohol (0.569 mL, 5.1 mmol) in THF (5 mL) was added PPh₃ (resin, 2.55 g, 7.65 mmol) followed by the addition of DIAD (1.48 mL, 7.65 mmol). The reaction mixture stirred at -10°C for 15 minutes under nitrogen. A solution of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one (1.0 g, 3.4 mmol), in DMF (10 mL) was added to the resin suspension. The reaction

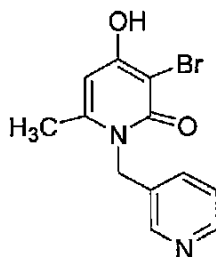
mixture stirred at 0° C for 1.5 hours and then allowed to stir at room temperature overnight. The resin was filtered and rinsed with fresh MeOH and the filtrate was concentrated. The residue was dissolved in ethyl acetate and purified by flash column chromatography (ethyl acetate). The appropriate fractions were concentrated. ¹H-NMR (CD₃OD, 400 MHz) δ 8.47 (d, 2H, J= 5.6 Hz), 7.63 (q, 1H), 7.15 (d, 1H, J= 5.6 Hz), 7.05 (m, 2H), 6.55 (s, 1H), 5.45 (s, 2H), 5.31 (s, 2H), 2.35 (s, 3H); ES-HRMS m/z 421.0366/423.0355 (M+H calculated for C₁₉H₁₆N₂O₂F₂Br requires 421.0358/423.0339).

Example 428



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step 1. Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

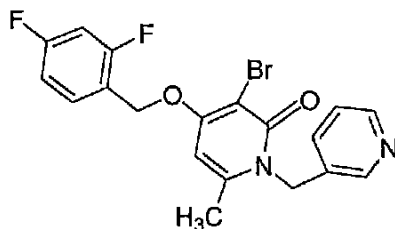


Commercially available 4-hydroxy-6-methyl pyrone (15 g, 119.0 mmol) was condensed with commercially available 3-(aminomethyl) pyridine (12.10 mL, 119.0 mmol) in water (75

mL). The mixture was heated in an oil bath at reflux for 1 hour under nitrogen. The solvent was evaporated. ¹H-NMR (CD₃OD, 400 MHz) δ 8.43 (d, 1H, J= 4.8 Hz), 8.38 (s, 1H), 7.60 (d, 1H, J= 8.0 Hz), 7.39 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 5.97 (d, 1H, J= 2.0 Hz), 5.79 (d, 1H, J= 2.4 Hz), 5.33 (s, 2H), 2.28 (s, 3H); ES-LRMS (M+H) m/z 217.

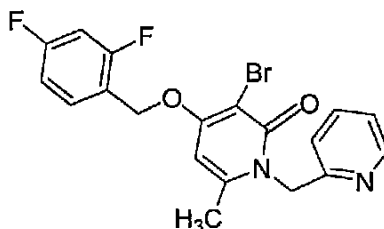
To a suspension of the above compound (5.01 g, 23.1 mmol) in MeCl₂ (50 mL) was added NBS (4.53 g, 25.4 mmol). The reaction mixture stirred at room temperature for 30 minutes under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh MeCl₂ and dried to afford a beige solid (7.89 g, 114%) after drying. ¹H-NMR (CD₃OD, 400 MHz) δ 8.44 (d, 1H, J= 4.4 Hz), 8.39 (s, 1H), 7.62 (d, 1H, J= 7.6 Hz), 7.39 (dd, 1H, J= 5.2 Hz, 4.4 Hz), 6.07 (s, 1H), 5.39 (s, 2H), 2.29 (s, 3H); ES-LRMS (M+H) m/z 295/297.

Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



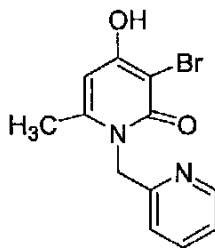
The compound was prepared essentially as described in Step 2 of example 424 using 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one. ¹H-NMR (CD₃OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 8.41 (s, 1H), 7.63 (m, 2H), 7.41 (dd, 1H, J= 5.2 Hz, 4.8 Hz), 7.02 (m, 2H), 6.52 (s, 1H), 5.44 (s, 2H), 5.29 (s, 2H), 2.40 (s, 3H); ES-HRMS m/z 421.0355/423.0358 (M+H calculated for C₁₉H₁₆N₂O₂F₂Br requires 421.0358/423.0339).

Example 435



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one

Step 1. Preparation of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one



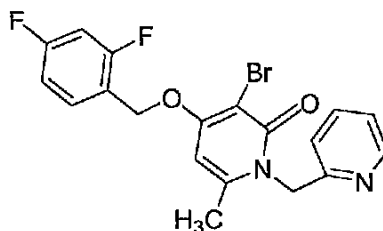
Commercially available 4-hydroxy-6-methyl pyrone (5 g, 39.6 mmol) was condensed with commercially available 2-(aminomethyl) pyridine (4.03 mL, 39.6 mmol) in water (25 mL). The mixture was heated in an oil bath at reflux for 1.5 hour under nitrogen. The solvent was evaporated. MS and ^1H -NMR were consistent with the desired desbromonated structure. ^1H -NMR (CD_3OD , 400 MHz) δ 8.47 (d, 1H, J = 4.8 Hz), 7.75 (ddd, 1H, J = 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.28 (dd, 1H, J = 4.8 Hz, 4.8 Hz), 7.11 (d, 1H, J = 7.6 Hz), 5.98 (d, 1H, J = 2.4 Hz), 5.77 (d, 1H, J = 2.4 Hz), 5.35 (s, 2H), 2.28 (s, 3H); ES-LRMS ($\text{M}+\text{H}$) m/z 217.

To a suspension of the above compound (3.0 g, 13.8 mmol) in MeCl_2 (30 mL) was added NBS (2.71 g, 15.18 mmol). The reaction mixture stirred at room temperature for 2.5 hours under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh MeCl_2 and dried to afford a beige solid (3.18 g, 77%) after drying. ^1H -NMR

(CD₃OD, 400 MHz) δ 8.46 (d, 1H, J= 4.8 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.29 (dd, 1H, J= 5.2 Hz, 5.2 Hz), 7.17 (d, 1H, J= 8.0 Hz), 6.07 (s, 1H), 5.40 (s, 2H), 2.30 (s, 3H); ES-LRMS (M+H) m/z 295/297.

5

Step 2. Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one

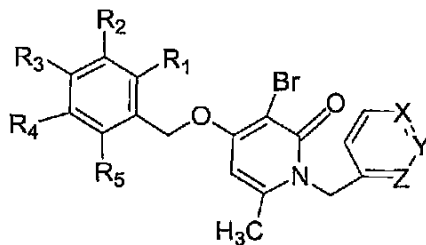


10

The compound was prepared essentially as described in Step 2 of example 424 using 3-bromo-4-hydroxy-6-methyl-1-(pyridin-2-ylmethyl)pyridin-2(1H)-one ¹H-NMR (CD₃OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 2.0 Hz, 1.6 Hz), 7.62 (q, 1H), 7.29 (dd, 1H, J= 5.2 Hz, 5.6 Hz), 7.21 (d, 1H, J= 8.0 Hz), 7.04 (m, 2H), 6.51 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.42 (s, 3H); ES-HRMS m/z 421.0354/423.0332 (M+H calculated for C₁₉H₁₆N₂O₂F₂Br requires 421.0358/423.0339).

15

20 Examples 425-427, 429-435, 436-437



The following compounds were prepared essentially according to the procedures set forth above for Example 424, using the products of Step 1 of Examples 424, 428, or 435.

Ex.No.	R ₁	R ₂	R ₃	R ₄	R ₅	X	Y	Z	MF	M+H m/z required	ES-HRMS m/z
425	H	H	F	H	H	N	CH	CH	C ₁₉ H ₁₆ N ₂ O ₂ FBr	403.0452/ 405.0434	403.0444 405.0414
426	F	H	F	H	F	N	CH	CH	C ₁₉ H ₁₄ N ₂ O ₂ F ₃ Br	439.0264/ 441.0245	439.0270 441.0274
427	F	H	H	H	F	N	CH	CH	C ₁₉ H ₁₅ N ₂ O ₂ F ₂ Br	421.0358/ 423.0339	421.0378 423.0368
429	H	H	F	H	H	CH	N	CH	C ₁₉ H ₁₆ N ₂ O ₂ FBr	403.0487/ 405.0438	403.0487 405.0438
430	F	H	F	H	F	CH	N	CH	C ₁₉ H ₁₄ N ₂ O ₂ F ₃ Br	439.0264/ 441.0245	439.0267 441.0241
431	F	H	H	H	H	CH	N	CH	C ₁₉ H ₁₆ N ₂ O ₂ FBr	403.0452/ 405.0434	403.0489 405.0474
432	F	H	F	F	H	CH	N	CH	C ₁₉ H ₁₄ N ₂ O ₂ F ₃ Br	439.0264/ 441.0245	439.0266 441.0231
433	F	H	Cl	H	H	CH	N	CH	C ₁₉ H ₁₅ N ₂ O ₂ FClBr	437.0062/ 439.0041	437.0068 439.0041
434	Cl	H	F	H	H	CH	N	CH	C ₁₉ H ₁₅ N ₂ O ₂ FClBr	437.0062/ 439.0041	437.0048 439.0043
435	F	H	H	H	F	CH	N	CH	C ₁₉ H ₁₅ N ₂ O ₂ F ₂ Br	421.0358/ 423.0339	421.0371 423.0336
436	H	H	F	H	H	CH	CH	N	C ₁₉ H ₁₆ N ₂ O ₂ FBr	403.0452/ 405.0434	403.0454 405.0379
437	F	H	F	H	F	CH	CH	N	C ₁₉ H ₁₄ N ₂ O ₂ F ₃ Br	439.0264/ 441.0245	439.0266 441.0242
438	F	H	F	F	H	CH	CH	N	C ₁₉ H ₁₄ N ₂ O ₂ F ₃ Br	439.0264/ 441.0245	439.0264 441.0242

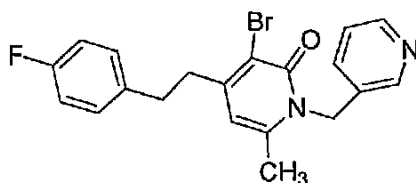
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NMR characterization of compounds of Examples 425-427, 429-435, 436-437

Ex.No.	NMR Data
425	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.47 (d, 2H, J= 5.6 Hz), 7.50 (q, 2H), 7.14 (m, 4H), 6.49 (s, 1H), 5.44 (s, 2H), 5.27 (s, 2H), 2.32 (s, 3H)
426	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.48 (dd, 2H, J= 1.6 Hz), 7.15 (d, 2H, J= 6.0 Hz), 6.98 (t, 2H, J= 1.2 Hz), 6.60 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.36 (s, 3H)

427	¹ H NMR (CD ₃ OD, 400 MHz) δ 8.47 (d, 2H, J = 1.6 Hz), 7.45 (m, 1H), 7.16 (d, 2H, J = 5.6 Hz), 7.06 (t, 2H, J = 8.4 Hz), 6.62 (s, 1H), 5.46 (s, 2H), 5.34 (s, 2H), and 2.37 (s, 3H)
429	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 8.40 (s, 1H), 7.62 (d, 1H, J= 8.0 Hz), 7.49 (q, 2H), 7.41 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.14 (t, 2H, J= 8.8 Hz), 6.46 (s, 1H), 5.43 (s, 2H), 5.26 (s, 2H), 2.38 (s, 3H)
430	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 3.6 Hz), 8.42 (d, 1H, J= 1.2 Hz), 7.60 (d, 1H, J= 8.4 Hz), 7.41 (dd, 1H, J= 5.2 Hz, 4.8 Hz), 6.97 (m, 2H), 6.57 (s, 1H), 5.45 (s, 2H), 5.27 (s, 2H), 2.42 (s, 3H)
431	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 8.41 (d, 1H, J= 1.6 Hz), 7.58 (m, 2H), 7.41 (m, 2H), 7.22 (m, 2H), 6.51 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 2.39 (s, 3H)
432	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.41 (d, 1H, J=1.6 Hz), 7.63 (d, 1H, J= 7.6 Hz), 7.53 (m, 1H), 7.41 (dd, 1H, J= 5.6 Hz, 5.2 Hz), 7.26 (m, 1H), 6.51 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.40 (s, 3H)
433	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.41 (d, 1H, J= 1.6 Hz), 7.60 (m, 2H), 7.39 (dd, 1H, J= 5.2 Hz), 7.28 (s, 1H), 7.26 (s, 1H), 6.50 (s, 1H), 5.44 (s, 2H), 5.31 (s, 2H), 2.40 (s, 3H)
434	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.41 (d, 1H, J= 1.6 Hz), 7.68 (m, 2H), 7.39 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.31 (dd, 1H, J= 2.4 Hz, 2.8 Hz), 7.16 (ddd, 1H, J= 2.8 Hz, 2.8 Hz, 2.8 Hz), 6.50 (s, 1H), 5.45 (s, 2H), 5.32 (s, 2H), 2.41 (s, 3H)
435	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.0 Hz), 8.42 (s, 1H), 7.60 (d, 1H, J= 8.0 Hz), 7.47 (m, 1H), 7.40 (dd, 1H, J= 5.2 Hz, 4.8 Hz), 7.07 (m, 2H), 6.59 (s, 1H), 5.45 (s, 2H), 5.32 (s, 2H), 2.41 (s, 3H)
436	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.8 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.51 (q, 2H), 7.30 (dd, 1H, J= 5.2 Hz), 7.19 (d, 1H, J= 7.6 Hz), 7.14 (t, 2H, J= 8.8 Hz), 6.46 (s, 1H), 5.44 (s, 2H), 5.26 (s, 2H), 2.40 (s, 3H)
437	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.46 (d, 1H, J= 4.8 Hz), 7.76 (ddd, 1H, J=2.0 Hz, 1.6 Hz, 1.6 Hz), 7.29 (dd, 1H, J= 4.8 Hz, 5.2 Hz), 7.21 (d, 1H, J= 7.6 Hz), 6.69 (dd, 2H, J= 8.0 Hz, 7.6 Hz), 6.57 (s, 1H), 5.46 (s, 2H), 5.28 (s, 2H), 2.43 (s, 3H)
438	¹ H-NMR (CD ₃ OD, 400 MHz) δ 8.45 (d, 1H, J= 4.4 Hz), 7.76 (ddd, 1H, J= 2.0 Hz, 1.6 Hz, 1.6 Hz), 7.55 (m, 1H), 7.26 (m, 3H), 6.50 (s, 1H), 5.46 (s, 2H), 5.29 (s, 2H), 2.42 (s, 3H)

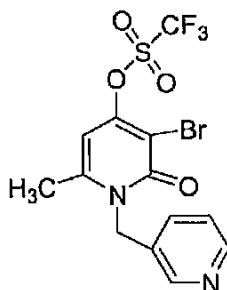
Example 439



5

3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

Step 1. Preparation of 3-bromo-6-methyl-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl trifluoromethanesulfonate



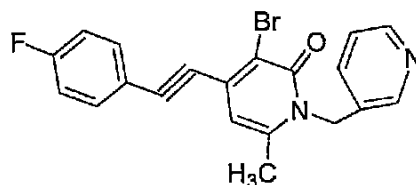
5

To a chilled suspension (-30° C) of 3-bromo-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (0.481g, 1.63 mmol) in dichloromethane (6 mL) was added triethylamine (0.28 mL, 2.04 mmol), followed by the addition of a solution of trifluoromethanesulfonic anhydride (0.4 mL, 2.44 mmol) in dichloromethane (3 mL). The reaction mixture stirred at -30° C under nitrogen for 1 hour. The reaction mixture was diluted with dichloromethane and washed with cold NaHCO₃/water. The organic extracts were dried over Na₂SO₄ and the filtrate was concentrated under reduced pressure to afford the desired compound as a yellow semisolid (0.6675 g, 95%) after drying. ES-LRMS (M+H) m/z 427.1/429.1.

10

Step 2. Preparation of 3-bromo-4-[(4-fluorophenyl)ethynyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

20



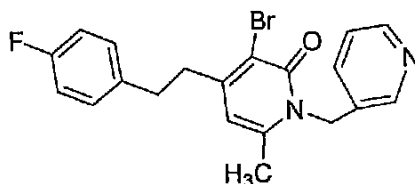
To a degassed solution of 3-bromo-6-methyl-2-oxo-1-(pyridin-3-ylmethyl)-1,2-dihydropyridin-4-yl trifluoromethanesulfonate (0.6675 g, 1.56 mmol) in DMF (9 mL),

25

DIEA (0.35 mL, 2.03 mmol), 4-fluorophenylacetylene (0.235 mL, 1.95 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (0.11g) were added. The reaction mixture stirred at room temperature under nitrogen for 1 hour and then heated in an oil bath (65°C) under nitrogen

5 overnight. The solvents were distilled in vacuo and the residue was purified by flash column chromatography (5% methanol in ethyl acetate). The extracts were concentrated to afford the desired compound (0.432 g, 69%) after drying. ^1H -NMR (CD_3OD , 400 MHz) δ 8.45 (s, 2H), 7.96 (s, 1H), 7.64 (m, 3H), 7.41 (dd, 1H, $J = 4.8$ Hz, 4.8 Hz), 7.18 (t, 2H, $J = 8.8$ Hz), 6.46 (s, 1H), 5.45 (s, 2H), 2.37 (s, 3H); ES-HRMS m/z 397.0361/399.0310 ($M+H$ calculated for $\text{C}_{20}\text{H}_{15}\text{N}_2\text{OFBr}$ requires 397.0346/399.0328).

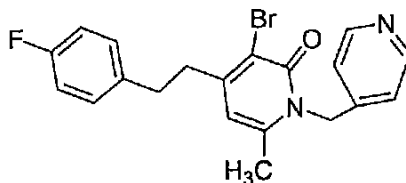
15 Step 3. Preparation of 3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



20 A suspension of 3-bromo-4-[(4-fluorophenyl)ethynyl]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (0.430 g, 1.01 mmol) in Ethyl acetate (5 mL) and EtOH (5 mL), containing PtO_2 (0.015 g) was stirred in an atmosphere of hydrogen (15 psi) in a Fischer-Porter bottle for 2 hours. The reaction mixture
25 was filtered and the filtrate was concentrated to reduce volume. The material was purified by flash column chromatography (ethyl acetate). The appropriate fractions were combined and concentrated under reduced pressure to afford the desired product (0.0943 g, 22 %) as a sticky
30 semisolid after drying. ^1H -NMR (CD_3OD , 400 MHz) δ 8.46 (d,

2H, J= 26.4 Hz), 7.60 (d, 1H, J= 8.0 Hz), 7.41 (dd, 1H, J= 4.8 Hz, 4.8 Hz), 7.21 (m, 2H), 6.97 (t, 2H, J= 8.8 Hz), 6.24 (s, 1H), 5.43 (s, 2H), 2.93 (m, 4H), 2.31 (s, 3H); ES-HRMS m/z 401.0645/403.0603 (M+H calculated for C₂₀H₁₉N₂OBr requires 401.0659/403.0641).

Example 440



10 3-bromo-4-[2-(4-fluorophenyl)ethyl]-6-methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one

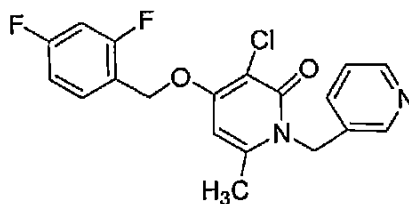
The title compound was prepared by a procedure similar to the one described for step 1 to step3 (0.374 g, 25%). MS and ¹H-NMR for step 1 were consistent with the desired structure.

15 ¹H-NMR (CD₃OD, 400 MHz) δ 8.80 (d, 2H, J= 6.8 Hz), 7.89 (d, 2H, J= 6.8 Hz), 6.61 (s, 1H), 5.66 (s, 2H), 2.45 (s, 3H); ES-HRMS m/z 427.9645/429.9625 (M+H calculated for C₁₃H₁₁N₂O₄SF₃Br requires 427.9599/429.9578).

20 MS and ¹H-NMR for step 3 were consistent with the desired structure. ¹H-NMR (CD₃OD, 400 MHz) δ 8.48 (d, 2H, J= 5.2 Hz), 7.21 (m, 2H), 7.13 (d, 2H, J= 5.2 Hz), 6.98 (t, 2H, J= 9.0 Hz), 6.26 (s, 1H), 5.43 (s, 2H), 2.95 (m, 4H), 2.25 (s, 3H); ES-HRMS m/z 401.0682/403.0636 (M+H calculated for C₂₀H₁₉N₂OBr requires 401.0659/403.0641).

25

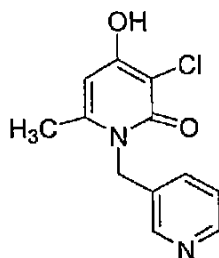
Example 441



3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

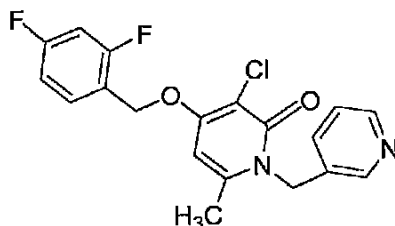
5

Step 1. Preparation of 3-chloro-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



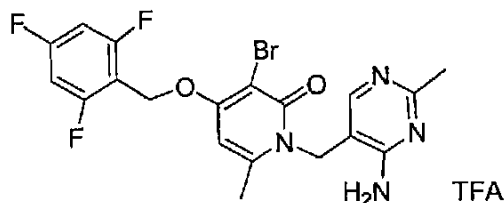
To a suspension of 4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (1.016 g, 4.7 mmol) in MeCl₂ (10 mL) was added NCS (1.21 g, 1.78 mmol). The reaction mixture stirred at room temperature for 24 hours under nitrogen. The suspension was chilled in an ice bath and filtered. The solid was washed with fresh MeCl₂ and dried to afford a yellow solid (1.00 g, 85%) after drying. ¹H-NMR (CD₃OD, 400 MHz) δ 8.54 (m, 2H), 7.85 (d, 1H, J=1.6 Hz), 7.61 (m, 1H), 6.10 (s, 1H), 5.41 (s, 2H), 2.33 (s, 3H); ES-LRMS (M+H) m/z 251/253.

Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one



To a degassed cold solution of DMF (10 mL) and PPh_3 (resin, 2.2 g, 6.6 mmol) was added DEAD (1.038 mL, 6.6 mmol). The reaction mixture stirred at -10°C for 20 minutes under nitrogen. A solution of 3-chloro-4-hydroxy-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one (1.00 g, 4.0 mmol) and 2,4-difluorobenzylalcohol (0.66 mL, 6.0 mmol) in DMF (10 mL) was added to the resin suspension. The reaction mixture stirred at -10°C for 30 minutes and then allowed to stir at room temperature for 1 hour. The resin was filtered and rinsed with fresh MeOH and the filtrate concentrated. The residue was dissolved in ethyl acetate and purified by flash column chromatography (5% methanol in ethyl acetate). The appropriate fractions were concentrated. $^1\text{H-NMR}$ (CD_3OD , 400 MHz) δ 8.45 (ddd, 2H, $J = 1.6\text{Hz}, 1.6\text{ Hz}, 1.6\text{ Hz}$), 7.61 (m, 2H), 7.41 (dd, 1H, $J = 4.4\text{ Hz}, 4.8\text{ Hz}$), 7.02 (m, 2H), 6.55 (s, 1H), 5.43 (s, 2H), 5.29 (s, 2H), 2.41 (s, 3H); ES-HRMS m/z 377.0882/379.0840 ($M+H$ calculated for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_2\text{F}_2\text{Cl}$ requires 377.0863/379.0840).

20 Example 442

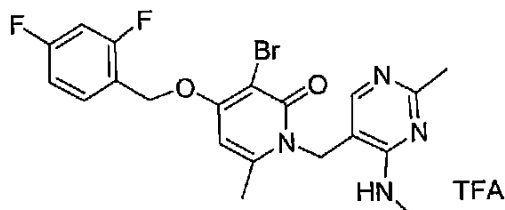


1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-6-methyl-4-[(2,4,6-trifluorobenzyl)oxy]pyridin-2(1H)-one trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 385, step 2 (0.142 g, 9%). ^1H NMR (CD_3OD , 400 MHz) δ 7.64 (s, 1H), 7.00 (m, 2H), 6.66 (s,

1H), 5.29 (s, 2H), 5.18 (s, 2H), 2.50 (s, 3H), 2.47 (s, 3H);
 ES-HRMS m/z 469.0488/471.0464 (M+H calculated for C₁₉H₁₇N₄O₂F₃Br
 requires 469.0481/471.0463).

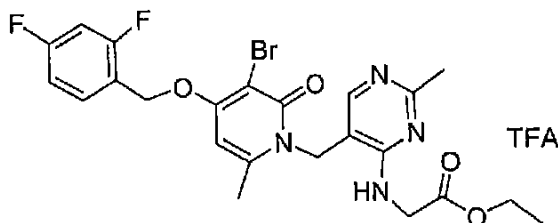
5 Example 443



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(2-methyl-4-
 (methylamino)pyrimidin-5-yl)methyl]pyridin-2(1H)-one
 10 trifluoroacetate

To a solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (0.15 g, 0.3 mmol) in
 15 DMF (3 mL) was added DBU (0.09 mL, 0.6 mmol). The solution
 was cooled in an ice bath and iodomethane (0.019 mL, 0.3 mmol)
 was added. The reaction mixture stirred at room temperature
 under nitrogen for 2 hours. The reaction was purified by
 reverse phase HPLC 10-90% CH₃CN/water (30 minute gradient) at
 20 a flow rate of 100 mL/min. The appropriate fractions (m/z=
 465 M+H) were combined and freeze dried to afford the desired
 product (0.036 g, 25%) as a white powder. ¹H NMR (CD₃OD, 400
 MHz) δ 7.72 (s, 1H), 7.60 (m, 1H), 7.03 (m, 2H), 6.62 (s, 1H),
 5.31 (s, 2H), 5.16 (s, 2H), 3.77 (s, 3H), 2.60 (s, 3H), 2.47
 25 (s, 3H); ES-HRMS m/z 465.0717/467.0712 (M+H calculated for
 C₂₀H₂₀N₄O₂F₂Br requires 465.0732/467.0714).

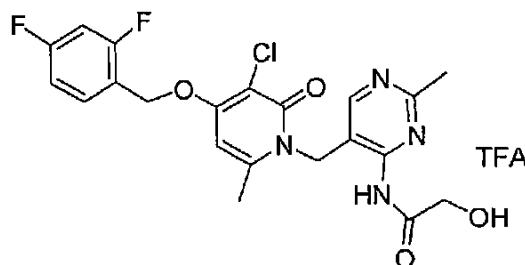
Example 444



ethyl N-(5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)glycinate
5 trifluoroacetate

The title compound was prepared by a procedure similar to the one described for Example 442 with the exception that the reaction mixture had to be heated at oil bath temperature 70°
10 C for 2 days (0.1384 g, 51 %). ¹H NMR (CD₃OD, 400 MHz) δ 7.78 (s, 1H), 7.61 (m, 1H), 7.03 (m, 2H), 6.61 (s, 1H), 5.30 (s, 2H), 5.18 (s, 2H), 5.03 (s, 2H), 4.27 (q, 2H), 2.55 (s, 3H), 2.46 (s, 3H), 1.28 (t, 3H, J = 7.0 Hz); ES-HRMS m/z 537.0936/539.0932 (M+H calculated for C₂₃H₂₄N₄O₄F₂Br requires
15 537.0943/539.0926).

Example 445

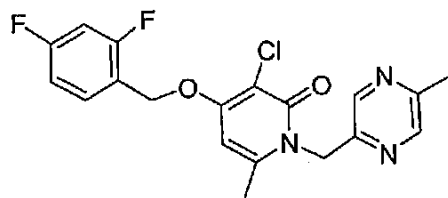


N-(5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-2-methylpyrimidin-4-yl)-
20 2-hydroxyacetamide trifluoroacetate

To a chilled solution of 1-[(4-amino-2-methylpyrimidin-5-yl)methyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one trifluoroacetate (0.200 g, 0.38 mmol)
25

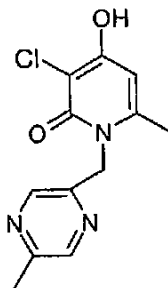
in DMF (20 mL) and a catalytic amount of DMAP was added triethylamine (0.064 mL, 0.38 mmol). The reaction stirred at -20° C and acetoxyacetyl chloride (0.082 mL, 0.76 mmol) was added. The reaction stirred cold for 15 minutes and then
5 allowed to warm up to room temperature for 3 hours. The reaction was monitored by LR-ESMS m/z = 466. The reaction was incomplete after 3 hours. Added acetoxyacetyl chloride (0.05 mL, 0.466 mmol), and triethylamine (0.2 mL, 1.43 mmol) to the reaction mixture and continued to stir overnight at room
10 temperature. The next morning the reaction heated at 65° C for 3 hours. The solvent was removed in vacuo and 1N LiOH (2.5 mL) was added to the residue. The reaction was heated at 60° C for 5 hours. The reaction was diluted with acetonitrile and water (1:1) and purified by reverse phase HPLC in 10-90%
15 CH₃CN/water (30 minute gradient) at a flow rate of 50 mL/min. The appropriate fractions were freeze dried to afford the desired product (0.020 g, 9%). ¹H NMR (CD₃OD, 400 MHz) δ 8.04 (s, 1H), 7.6 (m, 1H), 7.02 (m, 1H), 6.59 (s, 1H), 5.30 (s, 2H), 5.24 (s, 2H), 4.26 (s, 1H), 2.60 (s, 3H), 2.43 (s, 3H);
20 ES-HRMS m/z 465.1161 (M+H calculated for C₂₁H₂₀N₄O₄F₂Cl requires 465.1136).

Example 446



25 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

Step 1. Preparation of 3-chloro-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one



To a solution of 4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (1.00g, 4.3 mmol) in glacial acetic acid (10 mL) was added NCS (0.79 g, 5.94 mmol). The
5 reaction mixture stirred at 60° C for 6 hours. The solvent was removed under reduced pressure and the resulting residue was triturated with ethyl acetate. The desired product was filtered and dried (0.80 g, 69%). ¹H NMR (CD₃OD, 400 MHz) δ 8.47 (s, 1H), 8.42 (s, 1H), 6.08 (s, 1H), 5.36 (s, 2H), 2.50
10 (s, 3H), 2.43 (s, 3H); ES-HRMS m/z 266.0691 (M+H calculated for C₁₂H₁₃N₃O₂Cl requires 266.0691).

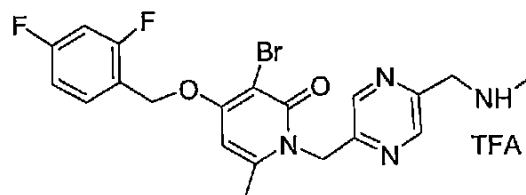
Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one

15

To a solution of 3-chloro-4-hydroxy-6-methyl-1-[(5-methylpyrazin-2-yl)methyl]pyridin-2(1H)-one (2.48 g, 9.3 mmol) in DMA (7 mL) was added K₂CO₃ (1.54 g, 11.0 mmol) followed by 2,4-difluorobenzyl bromide (1.2 mL, 9.3 mmol). The reaction
20 mixture stirred at room temperature under nitrogen for 1.5 hours. The solvent was distilled in vacuo. The resulting residue was diluted in dichloromethane and washed with water. The organic extracts were concentrated and the resulting residue was purified by flash column chromatography (ethyl
25 acetate). The appropriate fractions were combined, and concentrated. ¹H NMR (CD₃OD, 400 MHz) δ 8.49 (d, 1H, J=1.2 Hz), 8.40 (s, 1H), 7.59 (m, 1H), 7.04 (m, 2H), 6.54 (s, 1H),

5.41 (s, 2H), 5.28 (s, 2H), 2.54 (s, 3H), 2.40 (s, 3H); ES-HRMS m/z 392.1014 (M+H calculated for C₁₉H₁₇N₃O₂ClF₂ requires 392.0972).

5 Example 447



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[(5-[(methylamino)methyl]pyrazin-2-yl)methyl]pyridin-2(1H)-one trifluoroacetate

10

To a suspension of 3-bromo-1-[(5-(chloromethyl)pyrazin-2-yl)methyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.25 g, 0.53 mmol) in THF was added methylamine (1 mL, 2.1 mmol). The reaction was sealed and stirred at room temperature overnight. The reaction mixture was diluted in water:acetonitrile (1:1) and purified by reverse phase HPLC 10-90% CH₃CN/water (30 minute gradient) at a flow rate of 70 mL/min. The appropriate fractions were combined and freeze dried to afford the desired product (0.22 g, 71%) as an

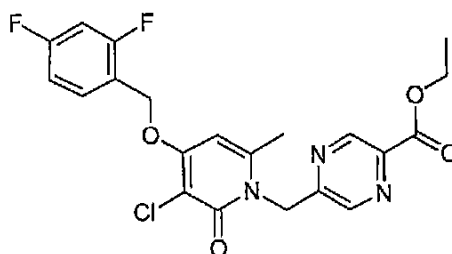
15

20

amorphous solid. ¹H NMR (CD₃OD, 400 MHz) δ 8.73 (s, 1H), 8.55 (s, 1H), 7.6 (m, 2H), 7.02 (m, 1H), 6.54 (s, 1H), 5.47 (s, 2H), 5.29 (s, 2H), 4.37 (s, 2H), 2.78 (s, 3H), 2.56 (s, 3H). ES-HRMS m/z 465.0732/467.0709 (M+H calculated for C₂₀H₂₀N₄O₂BrF₂ requires 465.0732/467.0714).

25

Example 448

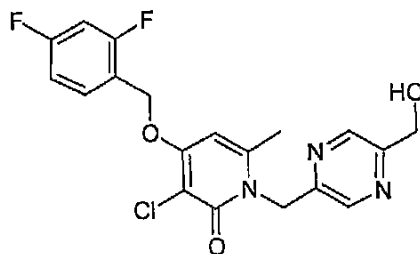


Ethyl 5-{ [3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-

5 yl]methyl}pyrazine-2-carboxylate

To a mixture of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.59 g, 2.07 mmol) and ethyl 5-(bromomethyl)pyrazine-2-carboxylate (0.62 g, 2.4 mmol) in THF (15 mL) was added NaH (0.06 g, 2.4 mmol).
10 The reaction stirred at 60° C for 3.5 hours. The solvent was removed under reduced pressure and the residue was partitioned over dichloromethane and citric acid (5%). The organic extracts were washed with water and dried over Na₂SO₄
15 (anhydrous). The organic extracts were concentrated and the residue was purified by flash column chromatography (100 % ethyl acetate). The appropriate fractions were combined and concentrated under reduced pressure to remove solvent. ¹H NMR (CD₃OD, 400 MHz) δ 9.11 (d, 1H, J= 1.6 Hz), 8.77 (s, 1H), 7.52 (m, 1H), 7.02 (m, 2H), 6.57 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 4.49 (q, 2H), 2.52 (s, 3H), 1.39 (t, 3H, J= 7.2 Hz); ES-
20 HRMS m/z 450.1045 (M+H calculated for C₂₁H₁₉N₃O₄ClF₂ requires 450.01027).

25 Example 449



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(5-(hydroxymethyl)pyrazin-2-yl)methyl]-6-methylpyridin-2(1H)-one

5

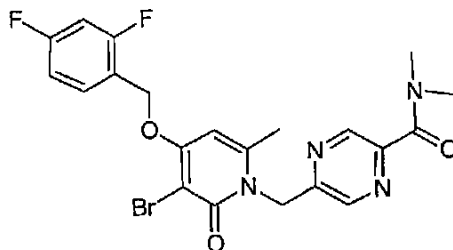
To a suspension of ethyl 5-[(3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl)methyl]pyrazine-2-carboxylate (4.0 g, 8.9 mmol) in THF:t-butanol (1:1) (10 mL) was added NaBH₄ (0.46 g, 12.4 mmol). The reaction stirred at room temperature under argon overnight. The reaction mixture was quenched with acetic acid (2 mL) and the solvent was removed in vacuo. The residue was triturated with water and filtered. The solid was washed with fresh water followed by ethanol. The solid was purified by flash column chromatography (100% ethyl acetate). The appropriate fractions were combined and concentrated under reduced pressure to afford the desired compound (1.58 g, 44%) as a white solid. ¹H NMR (CD₃OD, 400 MHz) δ 8.59 (s, 1H), 8.56 (s, 1H), 7.52 (m, 1H), 7.01 (m, 2H), 6.55 (m, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 4.71 (2H), 2.54 (s, 3H); ES-HRMS m/z 408.0940 (M+H calculated for C₁₉H₁₇N₃O₃ClF₂ requires 408.0921).

10

15

20

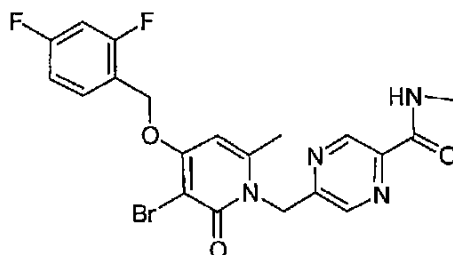
Example 450



5-{ [3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylpyrazine-2-carboxamide

To a cold solution of 5-{ [3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}pyrazine-2-carboxylic acid (0.175 g, 0.37 mmol) in DMF (5 mL, -10° C) was added IBCF (0.046 mL, 0.35 mmol) followed by NMM (0.041 mL 0.37 mmol). The reaction was activated for 20 minutes at -15° C after which dimethylamine (0.375 mL, 0.74 mmol) was added. The reaction stirred at -10° C to room temperature for 45 minutes. The solvent was removed in vacuo and the residue was purified by reverse phase HPLC 10-90% CH₃CN/water (30 minute gradient) at a flow rate of 70 mL/min. The appropriate fractions were combined and freeze dried to afford the desired product (0.140g, 75%) as a white solid. ¹H NMR (CD₃OD, 400 MHz) δ 8.68 (s, 1H), 8.67 (s, 1H), 7.52 (m, 1H), 7.02 (m, 2H), 6.54 (s, 1H), 5.50 (s, 2H), 5.30 (s, 2H), 3.11 (s, 3 H), 3.07 (s, 3H), 2.55 (s, 3H); ES-HRMS m/z 493.0680/495.0657 (M+H calculated for C₂₁H₂₀N₄O₃BrF₂ requires 493.0680/495.0657).

Example 451



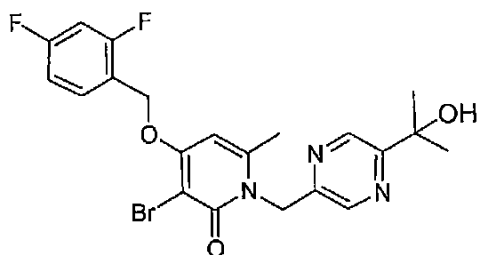
5-{ [3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-methylpyrazine-2-carboxamide

The title compound was prepared essentially as in Ex. 450, substituting dimethylamine with methylamine. ¹H NMR (CD₃OD, 400

MHz) δ 9.07 (s, 1H), 8.68 (s, 1H), 7.54 (m, 1H), 7.02 (m, 2H), 6.54 (s, 1H), 5.52 (s, 2H), 5.30 (s, 2H), 2.94 (s, 3H), 2.54 (s, 3H); ES-HRMS m/z 479.0542/481.0518 ($M+H$ calculated for $C_{20}H_{18}N_4O_3BrF_2$ requires 479.0525, 481.0507).

5

Example 452



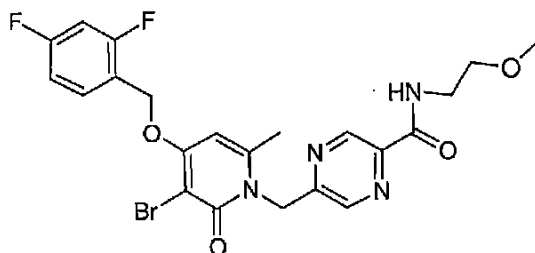
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[[5-(1-hydroxy-1-methylethyl)pyrazin-2-yl]methyl]-6-methylpyridin-2(1H)-one

10

To a cold flask of MeMgBr (1.59 mL, 1.0 mmol) was added a suspension of ethyl 5-[[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl]pyrazine-2-carboxylate (0.5 g, 1.0 mmol) in THF (20 mL). The reaction stirred at 0° C for 1.5 hours and then at room temperature overnight. The reaction was quenched with cold citric acid (25 mL, 5%) and extracted with ethyl acetate (2 X 100 mL). The organic extracts were washed with fresh water. The organic extracts were concentrated and purified by reverse phase HPLC 10-90% CH_3CN /water (30 minute gradient) at a flow rate of 70 mL/min. The appropriate fractions were combined and freeze dried to afford the desired product (29.9 mg, 6%). 1H NMR (CD_3OD , 400 MHz) δ 8.76 (d, 1H, J = 1.6 Hz), 8.54 (d, 1H, J = 1.2 Hz), 7.52 (m, 1H), 7.02 (m, 2H), 6.52 (s, 1H), 5.45 (s, 2H), 5.29 (s, 2H), 2.55 (s, 3H), 1.52 (s, 6H); ES-HRMS m/z 480.0745/482.0722 ($M+H$ calculated for $C_{21}H_{21}N_3O_3BrF_2$ requires 480.0729/482.0711).

25

Example 453



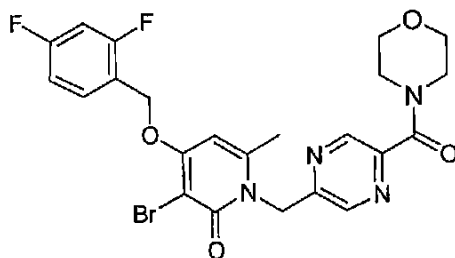
5 5-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-
1(2H)-yl]methyl}-N-(2-methoxyethyl)pyrazine-2-carboxamide

The title compound was prepared essentially as in Ex. 450,
substituting dimethylamine with 2-methoxyethylamine. ¹H NMR

10 (CD₃OD, 400 MHz) δ 9.08 (d, 1H, J= 1.2 Hz), 8.70 (d, 1H, J= 1.2
Hz), 7.61 (m, 1H), 7.04 (m, 2H), 6.54 (s, 1H), 5.53 (s, 2H),
5.30 (s, 2H), 3.56 (m, 4H), 3.30 (s, 3H), 2.54 (s, 3H); ES-
HRMS m/z 523.0822/525.0810 (M+H calculated for C₂₂H₂₂N₄O₄BrF₂
requires 523.0787/525.0770).

15

Example 454



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-{[5-(morpholin-
4-ylcarbonyl)pyrazin-2-yl]methyl}pyridin-2(1H)-one

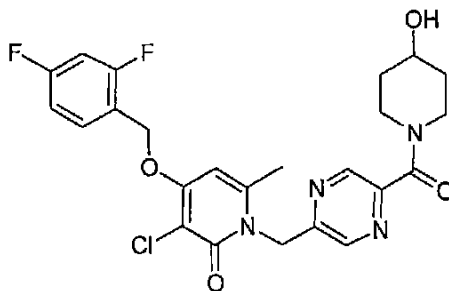
20

The title compound was prepared essentially as in Ex.
450, substituting dimethylamine with morpholine. ¹H NMR

(CD₃OD, 400 MHz) δ 8.77 (d, 1H, J= 1.6 Hz), 8.67 (s, 1H), 7.54
(m, 1H), 7.02 (m, 2H), 6.54 (s, 1H), 5.50 (s, 2H), 5.30 (s,

2H), 3.75 (s, 4H), 3.59 (dd, 4H, J= 5.6 Hz, 5.2 Hz), 2.55 (s, 3H); ES-HRMS m/z 535.0816/537.0817 (M+H calculated for C₂₃H₂₂N₄O₄BrF₂ requires 535.0787/537.0770).

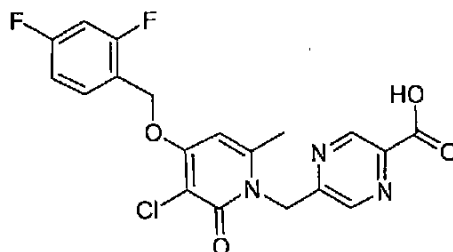
5 Example 455



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[(5-[(4-hydroxypiperidin-1-yl)carbonyl]pyrazin-2-yl)methyl]-6-methylpyridin-2(1H)-one

10

Step 1. Preparation of 5-[(3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl)methyl]pyrazine-2-carboxylic acid



15

A mixture of ethyl 5-[(3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl)methyl]pyrazine-2-carboxylate (1.03g, 2.3 mmol) in 1N NaOH (3.4 ml, 3.45 mmol, EtOH/water 1:1 v/v) stirred at room temperature for 2 hours. The reaction mixture was quenched with 5% citric acid and filtered. The solid was washed with water and dried to afford the desired product (1.011 g, 100%) as a white solid. ¹H NMR (CD₃OD, 400 MHz) δ 9.02 (s, 1H), 8.60 (s, 1H), 7.60 (m, 1H), 7.04 (m, 2H), 6.55 (s, 1H), 5.50

20

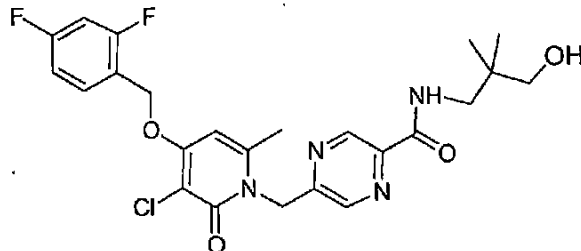
(s, 2H), 5.30 (s, 2H), 2.52 (s, 3H); ES-HRMS m/z 422.0732
(M+H calculated for C₁₉H₁₅N₃O₄ClF₂ requires 422.0714).

Step 2. Preparation of 3-chloro-4-[(2,4-difluorobenzyl)oxy]-
5 1-({5-[(4-hydroxypiperidin-1-yl)carbonyl]pyrazin-2-yl}methyl)-
6-methylpyridin-2(1H)-one

The title compound was prepared by a procedure similar to
the one described for Example 453 (0.1396 g, 47%). ¹H NMR
10 (CD₃OD, 400 MHz) δ 8.67 (s, 2H), 7.59 (m, 1H), 7.02 (m, 2H),
6.57 (s, 1H), 5.49 (s, 2H), 5.30 (s, 2H), 4.16 (m, 1H), 3.89
(septet, 1H), 3.72 (m, 1H), 3.38 (m, 2H), 2.56 (s, 3H), 1.93
(m, 1H), 1.83 (m, 1H), 1.45 (m, 2H); ES-HRMS m/z 505.1485 (M+H
calculated for C₂₄H₂₄N₄O₄ClF₂ requires 505.1449).

15

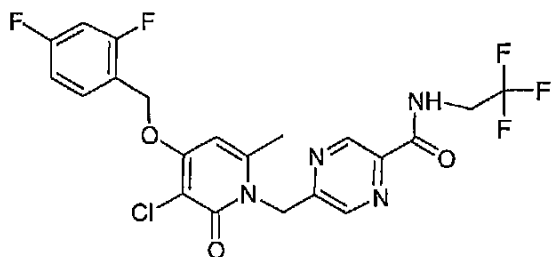
Example 456



5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-
oxopyridin-1(2H)-yl]methyl}-N-(3-hydroxy-2,2-
20 dimethylpropyl)pyrazine-2-carboxamide

The title compound was prepared by a procedure similar to
the one described for Example 455 (0.215 g, 71%). ¹H NMR
(CD₃OD, 400 MHz) δ 9.08 (d, 1H, J= 1.2 Hz), 8.71 (d, 1H, J= 1.6
25 Hz), 7.58 (m, 1H), 7.02 (m, 2H), 6.57 (s, 1H), 5.52 (s, 1H),
5.30 (s, 1H), 3.31 (s, 4H), 2.55 (s, 3H), 0.912 (s, 6H); ES-
HRMS m/z 507.1630 (M+H calculated for C₂₄H₂₆N₄O₄ClF₂ requires
507.1605).

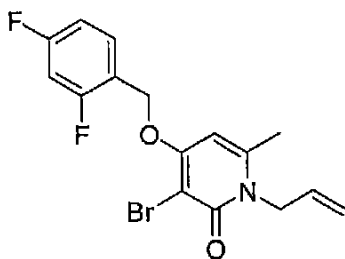
Example 457



5 5-{[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide

The title compound was prepared by a procedure similar to the one described for Example 455 except no purification was
 10 required, only a NaHCO₃/ethyl acetate extraction was needed (0.2176 g, 73%). ¹H NMR (CD₃OD, 400 MHz) δ 9.11 (d, 1H, J= 1.6Hz), 8.73 (d, 1H, J= 1.3 Hz), 7.59 (m, 1H), 7.02 (m, 2H), 6.57 (s, 1H), 5.53 (s, 2H), 5.30 (s, 2H), 4.01 (q, 2H), 2.54 (s, 3H); ES-HRMS m/z 503.0930 (M+H calculated for
 15 C₂₁H₁₇N₄O₃ClF₅ requires 503.0904).

Example 458



20 1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: 1-allyl-4-hydroxy-6-methylpyridin-2(1H)-one. 4-hydroxy-6-methyl-2-pyrone (2g, 16 mmol) was stirred in water (25 mL). Allylamine (1.2 mL, 16mmol) was added to the

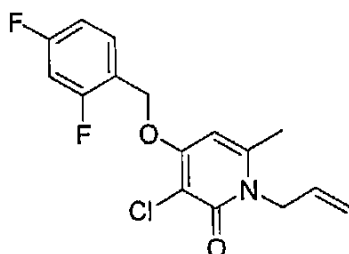
reaction. The reaction was then heated to 100 °C at which point the reaction became homogeneous. The reaction was stirred at 100 °C for 2h. The reaction was then allowed to cool to rt after which a white precipitate formed. The precipitate was isolated by suction filtration. After additional washing with water, 1.8g (69%) of an off-white solid was obtained.

Step 2: 1-allyl-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one. To a stirred solution of the above pyrone(4.0g, 24 mmol) in DMF(75ml) was added Cs₂CO₃ (7.8g, 24mmol) followed by addition of 2,4-difluorobenzyl bromide(3.4 mmol, 26.4 mmol). The resulting mixture was stirred at rt for 2h. Additional Cs₂CO₃ (1g) and bromide (1 ml) was added and the reaction was stirred for an additional 2h. The Cs₂CO₃ was removed by suction filtration. The DMF was removed under vacuum and the crude material was purified by flash chromatography. Elution with ethyl acetate-hexanes (2:1 to 1:1) afforded 1.5 g (21%) of the desired compound.

Step 3: 1-allyl-3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one. To a stirred suspension of the above pyridinone (1g, 3.4 mmol) in CH₃CN (10 ml) was added n-bromosuccinimide (670 mg, 3.8 mmol). The reaction mixture was stirred, at rt, for 3h. The product was obtained by filtration of the reaction mixture and washing of the solid with diethyl ether. ¹H-NMR (DMSO-d₆/400 MHz) δ 7.62 (app q, J = 8.8 Hz, 1H), 7.31 (ddd, J = 12.0, 9.6, 2.8 Hz, 1H); 7.15 (app dtd, J = 8.4, 2.4, 0.8 Hz, 1H); 6.50 (s, 1H); 5.87 (ddt, J = 12.4, 10.4, 5.6 Hz, 1H), 5.30 (s, 2H), 5.10 (dd, J = 10, 1.6 Hz, 1H), 4.87 (dd, J = 17.6, 1.6 Hz, 1H), 4.64 (m, 2H), 2.34 (s, 3H); ¹⁹F-NMR (DMSO-d₆/282.2 MHz) -109.68 (quin, J = 1H), -

113.66 (quar, $J = 1\text{H}$); HRMS m/z 370.0255 ($M + H$ calcd for $C_{16}H_{15}BrF_2NO_2 = 370.0246$).

Example 459



1-allyl-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one

Step 1: 1-allyl-3-chloro-4-hydroxy-6-methylpyridin-2(1H)-one.

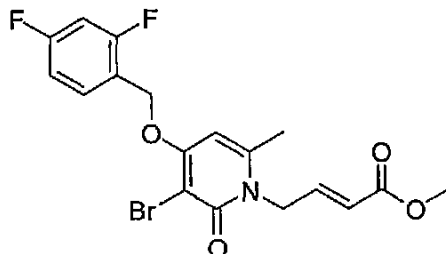
10 To a stirred solution of 1-allyl-4-hydroxy-6-methylpyridin-2(1H)-one (500 mg, 3.0 mmol) in CH_3CN (10 ml), at rt, was added sequentially n-bromosuccinimide (440 mg, 3.3 mmol) and dichloroacetic acid (546 μl , 6.62 mmol). The resulting mixture was stirred for 2h. The heterogeneous mixture was filtered
15 and the solid was washed with additional CH_3CN to give 350 mg (59%) of the desired product as a tan solid. $^1\text{H-NMR}$ ($DMSO_{d6}/300\text{ MHz}$) δ 11.16 (s, 1H), 5.98-5.86 (m, 2H), 5.12 (dd, $J = 10.5$, 1.5 Hz, 1H), 4.89 (dd, $J = 17.1$, 1.5 Hz, 1H), 4.63-4.61 (m, 2H), 2.29 (s, 3H). ES-HRMS m/z 200.050 ($M + H$ calcd for $C_9H_{11}ClNO_2 = 200.0470$)
20

Step 2: 1-allyl-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one. The title compound was prepared by the procedure outline in the synthesis of Example 458, step 3.

25 $^1\text{H-NMR}$ ($DMSO_{d6}/300\text{ MHz}$) δ 7.67 (app q, $J = 8.4\text{ hz}$, 1H), 7.36 (app dt, $J = 10.2$, 2.7 hz, 1H); 7.15 (m, 1H); 6.58 (s, 1H); 5.93 (ddt, $J = 15.3$, 9.6, 4.8 Hz, 1H), 5.30 (s, 2H) 5.15 (dd, $J = 10.2$, 1.2 Hz, 1H), 4.92 (dd, $J = 17.4$, 1.2 Hz, 1H), 4.69-

4.67 (m, 2H), 2.41 (s, 3H). ES-HRMS m/z 326.0760 (M + H calcd for $C_{16}H_{15}ClF_2NO_2$ = 326.0790).

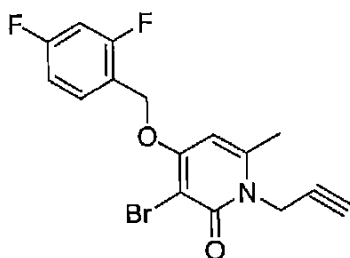
Example 460



Methyl (2E)-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]but-2-enoate

To a stirred suspension of NaH (277 mg, 11 mmol) in anhydrous THF (30 ml), which was cooled to 0°C, was slowly added 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (3.3g, 10 mmol). The resulting slurry was stirred for 15 min, after which methyl 4-bromocrotonate (1.4 ml, 12 mmol) was added to the reaction. The ice bath was removed and the reaction was heated to reflux for 16h. The reaction was quenched by the addition of 1N NH_4Cl . The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5x). The organics were combined, dried, and concentrated in vacuo. The crude yellowish material was then triturated with Et_2O to give, after filtration and drying, 1.8g (43%) of a white solid. 1H -NMR ($DMSO_{d6}$ /300 MHz) δ 7.65 (app q, J = 8.7 hz, 1H), 7.36 (app dt, J = 12.0, 3.0 hz, 1H); 7.17 (dt, J = 8.4, 1.8 Hz, 1H); 6.94 (dt, J = 15.9, 4.5 Hz, 1H); 6.57 (s, 1H), 5.52 (d, J = 15.9 Hz, 1H), 5.29 (s, 2H), 4.84 (m, 2H), 3.63 (s, 3H), 2.33 (s, 3H). ES-HRMS m/z 428.0301 (M + H calcd for $C_{18}H_{17}BrF_2NO_4$ = 428.0310).

Example 461

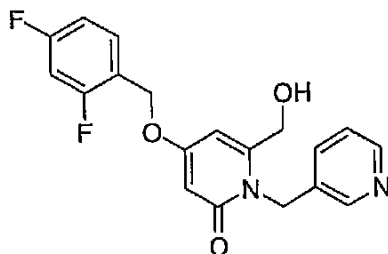


3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-
 5 ynylpyridin-2(1H)-one.

Step1: 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-prop-2-
 ynylpyridin-2(1H)-one. The title compound was prepared by
 alkylation of 4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-
 10 2(1H)-one (2.5g, 10 mmol) with propargyl bromide (1.3 ml, 11.0
 mmol) as described above to give 1.3g (44%) of the desired
 product. ¹H- NMR (DMSO_{d6}/300 MHz) δ 7.60 (app q, J = 8.4 hz,
 1H), 7.35-7.27 (m, 1H); 7.16-7.10 (m, 1H); 5.94 (d, J = 2.1
 Hz, 1H), 5.88 (d, J = 3.0 Hz, 1H), 5.03 (s, 2H), 4.76 (d, J =
 15 2.4, Hz, 2H), 3.31 (s, 3H), 3.24 (t, J = 2.4 Hz, 1H), 2.39 (s,
 3H); ES-HRMS m/z 290.0994 (M + H calcd for C₁₆H₁₄F₂NO₂ =
 290.0993).

Step 2: Bromination of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-
 20 prop-2-ynylpyridin-2(1H)-one (500 mg, 1.67 mmol) with NBS (300
 mg, 1.67 mmol) was carried out in the manner described above
 to give 350 mg (57%) of the desired compound. ¹H-NMR
 (DMSO_{d6}/300 MHz) δ 7.67 (app q, J = 9.0 hz, 1H), 7.36 (app dt,
 J = 10.5, 2.4 hz, 1H); 7.23-7.16 (m, 1H); 6.60 (s, 1H), 5.29
 25 (s, 2H), 4.90 (d, J = 2.4, Hz, 1H), 3.35 (s, 3H), 3.32 (s,
 1H), 2.53 (s, 3H); ES-HRMS m/z 368.0107 (M + H calcd for
 C₁₆H₁₃BrF₂NO₂ = 368.0098).

Example 462



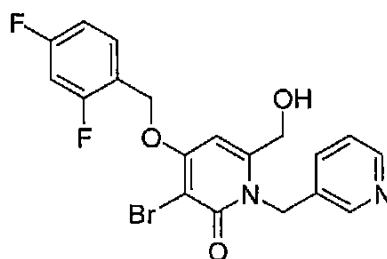
4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-
3-ylmethyl)pyridin-2(1H)-one.

Step1: To a suspension of (4-[(2,4-difluorobenzyl)oxy]-
6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one) (710 mg, 2
mmol) in dioxane (10 mL) was added selenium dioxide (1.1g 10
mmol). The resulting mixture was heated to 160 °C in a 125 mL
sealed tube for 1h. The reaction was filtered through a
fritted funnel. The filtrate was washed with (10:1) CH₂Cl₂-
MeOH. The organics were combined and concentrated in vacuo.
The crude material was purified by flash chromatography.
Elution with (50:50 → 0:100)hexanes yielded 450 mg (63%) of
the aldehyde. ¹H-NMR (DMSO-d₆/400 MHz). δ 9.48 (s, 1H, CHO).

Step 2: The aldehyde (350 mg, 1 mmol) was dissolved in MeOH
(4 mL) and cooled to 0 °C . To this mixture was added NaBH₄
(28 mg, 1 mmol) in one portion. After 30 min, additional NaBH₄
(20 mg) was added to the reaction. The MeOH was then removed
under vacuum. The residue was diluted with 1N NH₄Cl and then
extracted with CH₂Cl₂(4X). The organics were combined, dried,
and concentrated in vacuo. The yellowish crude product was
then taken up in (1:1) CH₂Cl₂-Et₂O. After sitting for a period
of time a white precipitate resulted. Filtration and washing
with additional Et₂O yielded, after drying, 250 mg (55%) of the
desired alcohol. ¹H-NMR (DMSO-d₆/400 MHz). δ 8.42 (dd, J = 4.4,

1.6 Hz, 1H) 8.37 (d, $J = 1.6$ Hz, 1H), 7.61 (app q, $J = 8.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.32-7.27 (m, 2H), 7.12 (dt, $J = 8.4$, 1.6 Hz, 1H), 6.07 (d, $J = 2.8$ Hz, 1H), 5.99 (d, $J = 12.8$ Hz, 1H), 5.63 (br s, 1H), 5.18 (s, 2H), 5.09 (s, 2H), 4.29 (s, 2H). LC/MS, $t_r = 1.19$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 359.1 (M+H)

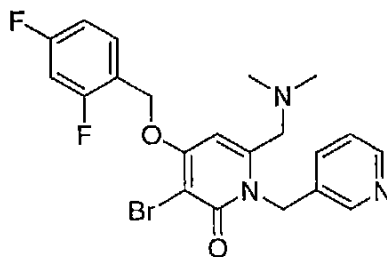
Example 463



3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-(hydroxymethyl)-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one.

The title compound was prepared by bromination of as described above to give a 60% yield. $^1\text{H-NMR}$ (DMSO-d_6 /300 MHz). δ 7.93 (d, $J = 7.8$ Hz, 1H), 7.73-7.65 (m, 3H), 7.38 (dt, $J = 10.2$, 2.4 Hz, 1H), 7.21 (app t, $J = 8.7$ Hz, 2H), 6.74 (s, 1H), 5.38.-5.36 (m, 4H), 4.50 (s, 2H); ES-HRMS m/z 437.0311 (M + H calcd for $\text{C}_{19}\text{H}_{16}\text{BrF}_2\text{N}_2\text{O}_2 = 437.0313$).

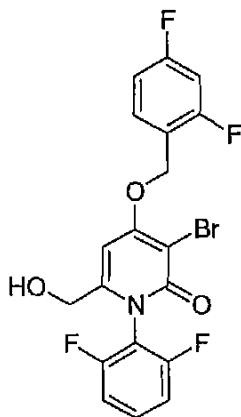
Example 464



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-
[(dimethylamino)methyl]-1-(pyridin-3-ylmethyl)pyridin-2(1H)-
one.

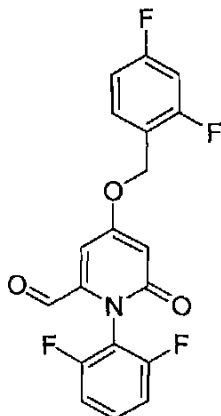
5 The title compound was prepared in a similar manner to the
procedure outlined below for 3-bromo-4-[(2,4-
difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-[(dimethylamino)-
methyl]pyridin-2(1H)-one using the aldehyde (300 mg, 0.85
mmol) described above and 2.0 N THF solution of dimethylamine
10 (500 μ L, 1 mmol) to give 110 mg (34%) of a colorless oil. The
oil was then dissolved in MeOH (1 mL) and stirred with fumaric
acid (25 mg) for 1h. The resulting precipitate was filtered,
washed with diethyl ether, and dried to give the pure product
as it's fumurate salt. $^1\text{H-NMR}$ (DMSO-d_6 /400 MHz). δ 8.43-8.41 (m,
15 1H), 8.35 (s, 1H), 7.67-7.61 (m, 1H), 7.44-7.40 (m, 1H), 7.35-
7.29 (m, 2H), 7.17-7.12 (m, 1H), 6.62 (s, 1H), 6.60 (s, 1H),
5.41 (s, 2H), 5.32 (s, 2H), 3.13 (s, 2H), 2.12 (s, 6H).
LC/MS, t_r = 1.55 minutes (5 to 95% acetonitrile/water over 5
minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z
20 464 (M+H).

Example 465



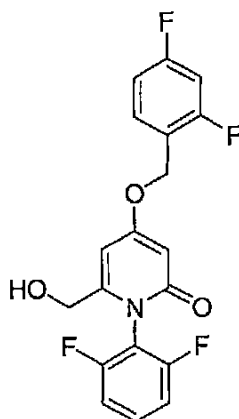
3-bromo-4- [(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one

Step1: 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde.



In a 300 ml high-pressure glass reaction vessel (16.3 g, 45 mmol) was dissolved in 1,4-dioxane (90 mL). The reaction vessel was sealed and immersed in a preheated oil bath at 170 ° C. The reaction was heated at 170° C (165 -170 °C) for 1.5 hours and then cooled to room temperature. The reaction was worked up by filtering the reaction mixture through a plug of celite and silica gel. The plug was then washed with 500 ml of methanol-CH₂Cl₂ mixture (1:5). The filtrate was evaporated to give 14.2 g of the desired crude aldehyde.

Step 2: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one.



In a 500 ml three neck round bottom flask equipped with a stir bar of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (14.2 g, 37.7 mmol) was dissolved in methanol (200 mL). The reaction mixture was cooled to 0 °C and to this was added sodium borohydride (2.13g, 56.30 mmol) in a slow portion-wise fashion. The reaction was stirred at 0 °C for 2 hour. Excess amount of sodium borohydride was added to drive the reaction to completion.

After stirring for approximately 2.5 hours, the reaction was allowed to warm to room temperature and then concentrated to dryness. The residue was taken up in ethyl acetate (100 mL) and washed with dilute HCl (pH of aqueous layer was approximately 4). Organic extracts were washed with brine (1X 50 ml), dried over MgSO₄, and concentrated in vacuo. The crude product was recrystallized from ethyl acetate and hexane to yield 7.56 g (44% yield-starting from step 1) of the desired alcohol.

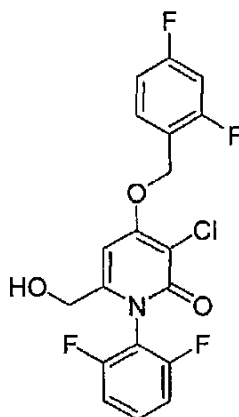
Step 3: Preparation of the title compound.

In a 100 ml round bottom flask of 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one (2.49 g, 6.56 mmol), from step 2, was dissolved in acetonitrile (35 mL). The reaction mixture was cooled to 0 °C in ice bath for 10 min. and then charged with N-bomosuccinamide (1.17g, 6.6 mmol). The mixture was allowed

to stir, at 0 °C, under nitrogen atmosphere for 2 hours. The reaction was the worked up by removing the acetonitrile under vacuum. The resulting residue was then filtered, with washing from a small amount of acetonitrile, to give a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 7.695 - 7.588 (m, 2H), 7.368-7.314 (m, 3H), 7.175 (dt, J = 8.5, 2.5, Hz, 1H), 6.760 (s, 1H), 5.712 (t, J = 5.674 Hz, 1H), 5.384 (s, 2H), 4.004-3.990 (m, 2H); ES-HRMS m/z 458.0013 (M+H-calcd for C₁₉H₁₃BrF₄NO₃, requires 458.0013).

10

Example 466



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one

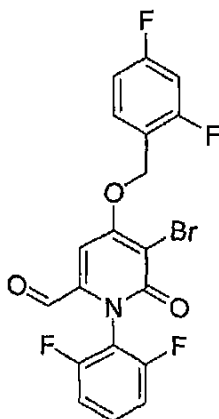
15

The title compound was prepared by taking 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-(hydroxymethyl)pyridin-2(1H)-one (1.5g, 3.9 mmol) in acetonitrile (15 mL) and adding to that N-chlorosuccinimide (580 mg, 4.3 mmol). The reaction was stirred at rt for 3h afterwhich a small amount of additional N-chlorosuccinimide (50 mg, 0.4 mmol) was added to the reaction. Stirring was continued for 1h. The reaction mixture was filtered through a fritted funnel to obtain the crude material. ¹H NMR (400 MHz, DMSO-d₆) δ 7.69 - 7.61 (m, 2H), 7.37-7.31 (m, 3H), 7.17 (dt, J

25

= 8.8, 2.0 Hz, 1H), 6.80 (s, 1H), 5.70 (t, J = 6.0 Hz, 1H), 5.38 (s, 2H), 4.01 (d, J = 6.0 Hz, 2H); ES-HRMS m/z 414.0515 (M+H calcd for C₁₉H₁₃ClF₄NO₃, requires 414.0520).

5 Example 467



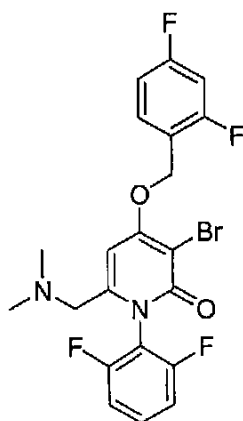
5-bromo-4-[(2,4-difluorobenzyl)oxy]
-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-
carbaldehyde

10

Preparation of the title compound. In a 50 ml one neck round bottom flask 4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0.36 g, 0.95 mmol) was dissolved in acetonitrile (5 mL). The reaction mixture was cooled to 0 °C in ice bath and charged with N-bromosuccinamide (0.17 g, 0.95 mmol). The mixture was allowed to stir at 0 °C for 2 hours under nitrogen atmosphere. After 2 hours, the solvent was evaporated under vacuum. ¹H NMR (400 MHz, DMSO-d₆) δ 9.53 (s, 1H), 7.73 - 7.67 (m, 2H), 7.62-7.54 (m, 1H), 7.35 (dt, J = 10.40, 2.56 Hz, 1H), 7.27 (t, J=8.35 Hz, 2H), 7.19 (dt, J =8.60, 2.44 Hz, 1H), 5.72 (s, 1H), 5.50 (s, 2H); ES-MS m/z 455.9836 (M+H calcd for C₁₉H₁₁BrF₄NO₃, requires 455.9859).

20

25 Example 468

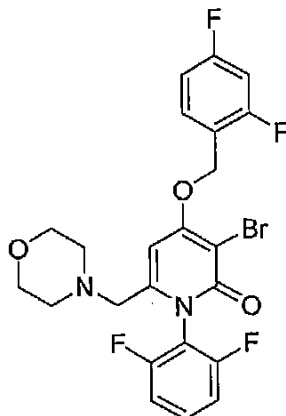


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-
[(dimethylamino)methyl]pyridin-2(1H)-one

5

In a 50 ml round bottom flask 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0.456 gm, 1.0 mmol) was stirred in dichloromethane (5 mL). To this mixture was added
10 a 2M THF solution of dimethyl amine (1.25ml, 2.5 mmol). The mixture was allowed to stir under nitrogen atmosphere and at room temperature for 2 hours. To this mixture was then added triacetoxy sodium borohydride (0.37 g, 1.75 mmol) followed by two to three drops of acetic acid. The mixture was then
15 stirred at rt overnight. The solvents were then removed by evaporation and the residue was taken up in ethyl acetate (30 ml) and washed with aqueous sodium bicarbonate and brine. The organics were then combined, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by flash column
20 chromatography using a solvent gradient of (3:1) ethyl acetate-hexane to (0:100) ethyl acetate to give 0.14 g (30 % yield) of the desired product. ¹H NMR (300 MHz, DMSO-d₆) δ 7.73-7.58 (m, 2H), 7.42-7.30 (m, 3H), 7.22 (dt, J=8.73, 2.60 Hz, 1H), 6.81 (s, 1H), 5.44 (s, 2H), 3.04 (s, 2H), 1.96 (s,
25 6H); ES-MS m/z 485.0 (M+H). ES-HRMS m/z 485.0457 (M+H calcd for C₂₁H₁₈BrF₄N₂O₂, requires 485.0489).

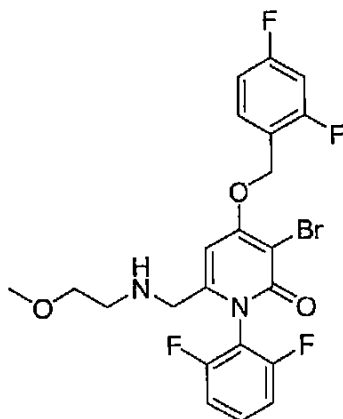
Example 469



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-
 5 (morpholin-4-ylmethyl)pyridin-2(1H)-one

The title compound was prepared by reacting 5-bromo-4-
 [(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-
 dihydropyridine-2-carbaldehyde (0.456 g, 1mmol) with
 10 morpholine (0.13 ml, 1.5 mmol) and triacetoxy sodium
 borohydride (0.42 g, 2.0 mmol) in dichloromethane (7 mL) by
 using a similar procedure to the one described for Example
 468. The crude product was purified by flash column
 chromatography. Elution with (50:50 → 0:100) hexanes-ethyl
 15 acetate to give 0.15 g (29% yield) of the desired product. ¹H
 NMR (300 MHz, DMSO-d₆) δ 7.75- 7.57 (m, 2H), 7.43-7.31 (m, 3H),
 7.20 (dt, J=8.64, 2.48 Hz, 2H), 6.85 (s, 1H), 5.44 (s, 2H),
 3.37 (app t, J=4.37 Hz, 4H), 3.13 (s, 2H), 2.08 (t, J=4.19 Hz,
 4H); ES-HRMS m/z 527.0600 (M+H calcd for C₂₃H₂₀BrF₄N₂O₃ requires
 20 527.0594).

Example 470



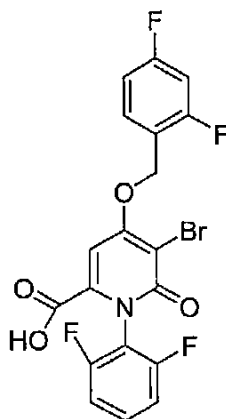
3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (2-methoxyethyl)amino methyl pyridin-2(1H)-one

5

The title compound was prepared by reacting 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (0.319 g, 0.7 mmol) with 2-methoxy ethylamine (0.086 ml, 1.0 mmol) and triacetoxysodium borohydride (0.42 g, 2.0 mmol) in dichloromethane (4 mL) by using a procedure, similar to the one described for Example 468. The crude product was purified by flash column chromatography. Elution with (50:50 → 0:100) hexanes-ethyl acetate to give 0.13 g of the desired product.

¹H NMR (400 MHz, CDCl₃) δ 7.54 (q, J=6.89 Hz, 1H), 7.41 - 7.33 (m, 1H), 7.19 (s, 1H), 6.99 (t, J = 7.90 Hz, 2H), 6.90 (dt, J=7.90, 2.78, Hz, 1H), 6.80 (dt, J = 10.60, 2.34 Hz, 1H), 6.51 (s, 1H), 5.24 (s, 2H), 3.33 (t, J=4.69 Hz, 1H), 3.30 (s, 3H), 2.57 (t, J= 4.86 Hz, 2H), 1.53 (s, 2H); ES-HRMS m/z 515.0548 (M+H calcd for C₂₂H₂₀BrF₄N₂O₃, requires 515.0594).

Example 471

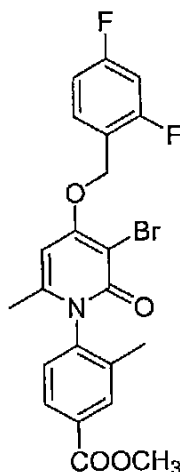


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid

5

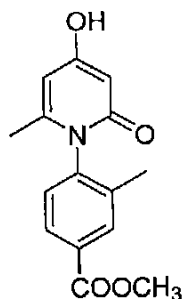
In a 100 ml round bottom flask, 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-oxo-1,6-dihydropyridine-2-carboxylic acid (1.70 g, 3.7 mmol) was dissolved in acetone (10 mL) and cooled to 0 °C in ice bath. To the reaction was added 1M acetone solution of Jones (5 ml, excess amount). Additional Jones reagent was added over time (approximately 6 hours) until the reaction was complete. The reaction was then concentrated down to dryness. The residue was then taken up in ethyl acetate (10 mL) and washed with brine. The dark yellow to brown colored crude product was purified by dissolving in 1N aqueous NaOH. The remaining organic impurities were removed by extracting with diethyl ether. The organic layers were discarded and the aqueous layer was acidified with dilute HCl (til pH app 1) to precipitate the pure acid which was then filtered and triturated with ether to obtain 1.17 g (65%) of the desired product. ¹H NMR (400 MHz, DMSO-d₆) δ 7.66 (q, J= 9.41 Hz, 1H), 7.57- 7.50 (m, 1H), 7.34 (dt, J= 10.11, 2.78 Hz, 1H), 7.28- 7.23 (m, 3H), 7.18 (dt, 8.90, 2.42 Hz, 1H), 5.47 (s, 2H). ES-
HRMS m/z 471.9814 (M+H calcd for C₁₉H₁₁BrF₄NO₄, requires 471.9808)

Example 472



Methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-
 5 oxopyridin-1(2H)-yl]-3-methylbenzoate

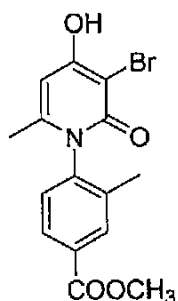
Step1: Preparation of methyl 4-(4-hydroxy-6-methyl-2-
 oxopyridin-1(2H)-yl)-3-methylbenzoate .



10 In a 50 ml one neck round bottom flask equipped with a
 stir bar, Dean Stark trap, and condenser 4-amino-2-methyl-
 methylbenzoate (1.19g, 11.63 mmol) and 4-hydroxy-6-methyl-2H-
 pyran-2-one (1.611g, 12.78 mmol) were mixed together and
 dissolved in 1,2-dichlorobenzene (5 mL). The mixture was
 15 vigorously stirred and then placed in a preheated oil bath at
 165 0 °C. The reaction was maintained at 165 0 °C for 1.5
 hour and cooled to room temperature. The reaction was worked
 up by diluting with toluene (10 mL) and then stirring at room
 temperature for 2 hours. A light brown precipitate resulted.
 20 The crude product was isolated by filtration and then

trituted with ether. ^1H NMR (400 MHz, DMSO- d_6) δ 10.64 (s, 1H), 7.93 (s, 1H), 7.85 (dd, 8.46 Hz, 1H), 7.26 (d, J = 8.12 Hz, 1H), 5.91 (d, J = 2.32 Hz, 1H), 5.54 (d, J = 2.32 Hz, 1H), 3.84 (s, 3H), 1.99 (s, 3H), 1.73 (s, 3H). ES-HRMS m/z 272.0880 (M-H calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_4$, requires 272.1001).

Step 3: Preparation of Methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate



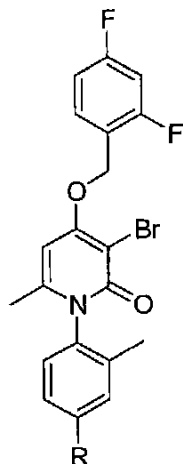
Methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate was prepared by reacting - methyl 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate with N-bomosuccinamide in acetonitrile by following a procedure, similar to the one described in Example 465- step 3. ^1H NMR (400 MHz, DMSO- d_6) δ 7.95 (s, 1H), 7.87 (dd, J = 7.76, 2.02 Hz, 1H), 7.31 (d, J = 8.54, 1H), 6.09 (s, 1H), 3.85 (s, 3H), 1.99 (s, 3H), 1.74 (s, 1H). ES-HRMS m/z 352.0195 (M+H calcd for $\text{C}_{15}\text{H}_{14}\text{BrNO}_4$, requires 352.0185)

Step 4: The title compound was prepared by taking methyl 4-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate (0.92 g, 2.61 mmol) and dissolving in dry DMF (5 mL). Potassium carbonate (0.432 g, 3.13 mmol) and 2,4-Difluorobenzyl bromide (0.335 ml, 2.61 mmol) were then added. The mixture was allowed to stir at room temperature for 2 hours.

The reaction was then worked up by pouring it into 100 ml of ice-water which resulted in a precipitate forming which was isolated by filtering through a fritted funnel. The crude product was washed with ether and dried in vacuum to give 0.85

5 g (76.20%) of pure product. ^1H NMR (400 MHz, DMSO- d_6) δ 7.98 (d, J = 1.6 Hz, 1H), 7.88 (dd, J = 8.04, 2.0 Hz, 1H), 7.69 (q, J = 8.6 Hz, 1H), 7.36-7.30 (m, 2H), 7.17 (dt, J = 8.7, 2.3 Hz, 1H), 6.71 (s, 1H), 5.32 (s, 2H), 3.86 (s, 3H), 2.00 (s, 3H), 1.86 (s, 3H). ES-HRMS m/z 478.0459 ($M+H$ calcd for $\text{C}_{22}\text{H}_{19}\text{BrF}_2\text{NO}_4$ requires 478.0466).

Examples 473-476



15 The compounds of Examples 473-476 are prepared by derivitization of the compounds of Example 472.

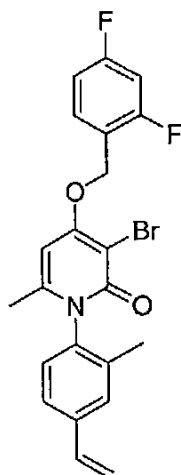
Compound No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 473	-CO ₂ H	C ₂₁ H ₁₆ BrF ₂ NO ₄	464.0310	464.0324
Ex. 474	-CH ₂ OH	C ₂₁ H ₁₈ BrF ₂ NO ₃	450.0500	450.0517
Ex. 475	C(O)NH(CH ₂) ₂ OCH ₃	C ₂₄ H ₂₂ BrF ₂ N ₂ O ₄	521.0888	521.0865
Ex. 476	C(O)NHCH ₃	C ₂₂ H ₂₀ BrF ₂ N ₂ O ₃	477.0626	477.0609

NMR characterization of compounds of Examples 473-476

Ex.No.	NMR Data
473	¹ H-NMR (400 MHz, DMSO-d ₆) δ 13.11 (s, 1H), 7.95 (d, J = 1.70 Hz, 1H), 7.86 (dd, J=7.88, 1.91 Hz, 1H), 7.67 (dq, J = 8.47, 1.89 Hz, 1H), 7.36-7.30 (m, 2H), 7.17 (dt, J =8.54, 2.48 Hz, 1H), 6.71 (s, 1H), 5.32 (s, 2H), 1.99 (s, 3H), 1.87 (s, 3H)
474	¹ H NMR (400 MHz, DMSO-d ₆) δ 7.67 (q, J =8.5 Hz, 1H), 7.34 (dd, J =10.04, 2.77 Hz, 1H), 7.32 (s, 1H), 7.24 (dd, J = 8.39, 1.47 Hz, 1H), 7.17 (dt, J = 8.84, 2.6 Hz, 1H), 7.08 (d, J = 7.94 Hz, 1 H), 6.66 (s, 1H), 5.30 (s, 2H), 5.25 (t, J = 6.01 Hz, 1H), 4.5 (d, J =6.68 Hz, 2H), 1.91 (s, 3H), 1.86 (s, 3H)
475	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.58 (app t, J =5.4 Hz, 1H), 7.84 (s, 1H), 7.76 (dd, J= 8.06, 1.63 Hz, 1H), 7.68 (dq, J= 8.77, 2.04 Hz, 1H), 7.33 (dt, J=9.76, 2.03 Hz, 1H), 7.27 (d, J=8.34 Hz, 1H), 7.17 (ddt, J=8.51, 2.63, 0.91 Hz, 1H), 6.70 (s, 1H), 5.31 (s, 2H), 4.50 (t, J=5.6 Hz , 1H), 3.47-3.36 (m, 4H), 3.24 (s, 3H), 1.97 (s, 3H), 1.87 (s, 3H)
476	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.50-8.49 (m, 1H), 7.82 (s, 1H), 7.74 (dd, J=8.22, 1.79 Hz, 1H), 7.69 (q, J= 6.75 Hz, 1H), 7.33 (dt, J= 9.88, 2.57 Hz, 1H), 7.26 (d, J=8.52 Hz, 1H), 7.17 (dt, J= 8.93, 2.16 Hz, 1H), 6.69 (s, 1H), 5.31 (s, 2H), 2.77 (d, J= 4.58 Hz, 3H), 1.97 (s, 3H), 1.86 (s, 3H)

5

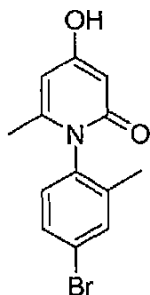
Example 477



3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one

10

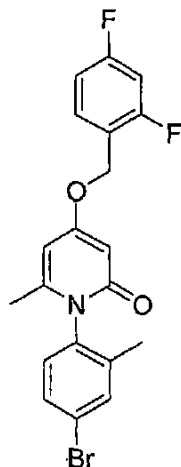
Step 1- Preparation of -1-(4-bromo-2-methylphenyl)-4-hydroxy-6-methylpyridin-2(1H)-one



The title compound was prepared in a similar manner to the procedure outlined above for 4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-3-methylbenzoate. ¹H NMR (400 MHz, DMSO-d₆) δ 10.61 (s, 1H), 7.59 (d, J= 2.84 Hz, 1H), 7.45 (dd, J= 8.39, 2.44 Hz, 1H), 7.06 (d, J= 7.44, 1H), 5.89 (d, J=2.73 Hz, 1H), 5.53 (d, J=2.30, 1H), 1.91 (s, 3H), 1.75 (s, 3H). ES-
 5 HRMS m/z 294.0127 (M+H calcd for C₁₃H₁₃BrNO₃, requires 294.0130).

10

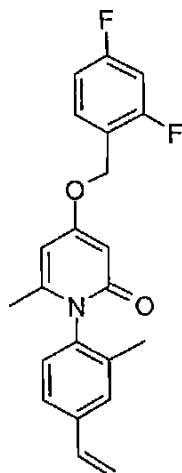
Step 2- Preparation of - 1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one



1-(4-bromo-2-methylphenyl)-4-hydroxy-6-methylpyridin-2
 15 (1H)-one (7.35 g, 25.0 mmol) was dissolved in DMF (15 mL) and stirred with potassium carbonate (4.14 g, 30.0 mmol) and 2,4 difluorobenzyl bromide (3.21 ml (25.0 mmol) at room temperature for 2 hours. The reaction was worked up by pouring in to 300 ml ice water under continuous stirring. A white
 20 precipitate was obtained which was isolated by filtering and

further purified by triturating with ether to give 3.06 g (29%) of the desired product. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.65-7.59 (m, 2H), 7.49 (dd, $J=8.45, 2.22$ Hz, 1H), 7.31 (dt, $J=9.79, 2.22$ Hz, 1H), 7.16- 7.08 (m, 2H), 6.05 (d, $J= 2.58$ Hz, 1H), 5.93 (d, $J= 2.66$ Hz, 1H), 5.08 (s, 2H), 1.93 (s, 3H), 1.77 (s, 3H). ES-HRMS m/z 420.0390 ($M+H$ calcd for $\text{C}_{20}\text{H}_{17}\text{BrF}_2\text{NO}_2$, requires 420.0411).

Step 3: Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one.



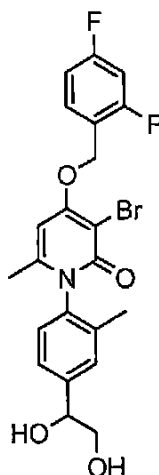
In a 50 ml round bottom flask previously evacuated and filled with nitrogen, 1-(4-bromo-2-methylphenyl)-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (0.420 g, 1.0 mmol) was dissolved in dry THF (10 mL). To this mixture was added $\text{Pd}(\text{PPh}_3)_4$ (0.173 g, 0.15 mmol). The reaction flask was sealed with a rubber septum, evacuated and filled with nitrogen. Under a nitrogen atmosphere, tributyl(vinyl)tin (0.35 ml, 1.2 mmol) was added to the sealed reaction mixture and stirred overnight at 50 $^\circ\text{C}$.

The reaction was worked up by quenching with water and extraction of the product with ethyl acetate. The crude product was purified by column chromatography. Elution with

ethyl acetate-hexanes (50:50 → 0:100) gave 0.32 g (69%) of the desired product.

Step 4: The title compound was prepared by reacting
 5 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one (0.64 g, 1.74 mmol) with N-bromosuccinamide (0.325 g, 1.83 mmol) in acetonitrile (9 mL) at 0°C using a similar procedure as described in step 3 of Example 465, to give 0.423 g (54.5 % after recrystallization)
 10 of the desired product. ¹H NMR (400 MHz, DMSO-d₆) δ 7.67(app q, J= 7.59 Hz, 1H), 7.48(s, 1H), 7.42(dd, J=8.21, 1.98 Hz, 1H), 7.33(dt, J=10.00, 2.27 Hz, 1H), 7.17(dt, J=8.51, 2.44 Hz, 1H), 7.13(d, J=7.88 Hz, 1H) 6.74(dd, J=11.29, 6.34 Hz, 1H), 6.67(s, 1H), 5.88(d, J= 17.85, 1H), 5.32-5.30 (m, 2H), 1.92 (s, 3H), 1.88 (s, 3H). ES-HRMS m/z 446.0579 (M+H calcd for C₂₂H₁₉BrF₂NO₂, requires 446.0568).

Example 478

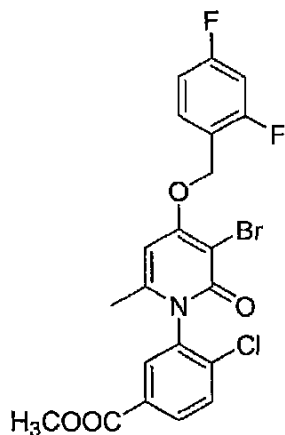


20 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[4-(1,2-dihydroxyethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(2-methyl-4-vinylphenyl)pyridin-2(1H)-one (0.126 g, 0.28 mmol) was

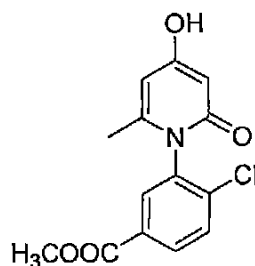
dissolved in a mixture of acetone (3 mL) and water (1 mL). To this was added 4-methylmorpholine N-oxide (0.032 g, 0.28 mmol) and catalytic amount (approximately 5 mgs) of osmium tetroxide was added, and stirred under nitrogen atmosphere. After
 5 approximately 2 hours, the reaction was worked up by evaporation of the acetone. The product was extracted into ethyl acetate and concentrated to give a dark colored solid which was further purified by column chromatography to give 0.049 g (37 % yield) of charcoal colored solid. ¹H NMR (400
 10 MHz, DMSO-d₆) δ 7.67 (q, J=8.24 Hz, 1H), 7.37-7.23 (m, 3H), 7.17 (dt, J= 8.62, 2.62 Hz, 1H), 7.07 (dd, J=9.36, 2.24 Hz, 1H), 6.65(s,1H), 5.30 (s, 2H), 4.74(t, J=6.16Hz, 1H), 4.57-4.50 (m, 1H), 3.45(app t, J=6.12 Hz, 2H), 3.41- 3.37 (m, 1H), 1.91(s,3H), 1.85 (s, 3H). ES-HRMS m/z 480.0625 (M+H calcd for
 15 C₂₂H₂₁BrF₂NO₄, requires 480.0623).

Example 479



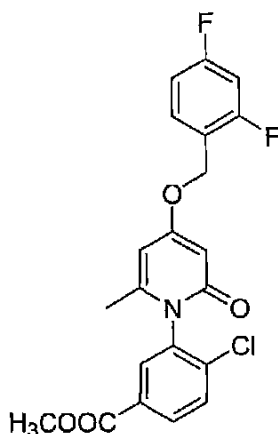
methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)
 20 oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoate

Step 1: Preparation of methyl 4-chloro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate.



A condensation reaction with methyl 3-amino-4-chlorobenzoate (14.5g, 78.2 mmol) and 4-hydroxy-6-methyl pyranone under
 5 reaction condition similar to the one described in Example 465- step 3 gave 12.32 (53.8%) of desired product.

Step-3- Preparation of methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate.



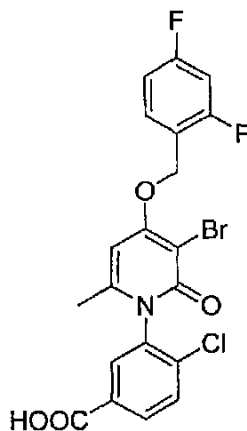
10

In a 250ml round bottom flask, methyl 4-chloro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (5.28 g, 18.0 mmol) from step1 was reacted with 2,4-difluoro-benzylbromide (3.72 g, 18.0 mmol) in DMF using similar procedure as in
 15 Example 472 step 3. After aqueous work up and chromatographic purification, 2.3 g (30%) pure product was obtained.

Step 4: methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoate was prepared
 20 by reacting methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (2.3 g, 5.47 mmol) with

N-bromosuccinamide (0.97 g, 5.47 mmol) in acetonitrile (10 mL) at 0°C, using a similar procedure as described in step 3 of Example 465, to give 1.80g (66.2 %) of the desired product. ¹H NMR (400 MHz, DMSO-d₆) δ 8.06-8.03 (m, 2H), 7.86 (d, J=9.70 Hz, 1H), 7.68 (q, J= 7.62, 1H), 7.34(dt, J=10.07, 2.46 Hz, 1H), 7.17 (dt, J= 8.72, 2.90 Hz, 1H), 6.73 (s, 1H), 5.33 (s, 2H), 3.85 (s, 3H), 1.91 (s, 3H). ES-MS m/z 495.9757 (M-H calcd for C₂₁H₁₄BrClF₂NO₄, requires 495.9795).

10 Example 480

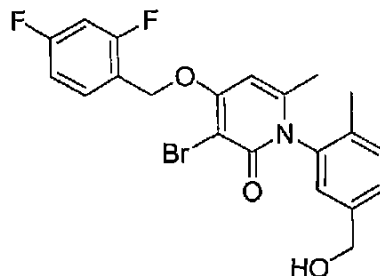


3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-chlorobenzoic acid

15 In a 50 ml round bottom flask, methyl-4-chloro-3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (0.450 g, 0.90 mmol) was stirred in THF (5 mL). To this mixture was added NaOH (0.120 g, 3.0 mmol) as a solution in water (1.5 mL). The reaction mixture was stirred
20 at room temperature overnight. The THF was evaporated and the residue was acidified with dilute HCl. A white precipitate was obtained. The product was filtered, washed with water and dried in vacuum to give 0.375 g (86 % yield) of the desired product. ¹H NMR (400 MHz, DMSO-d₆) δ 7.89 (dd, J=7.78, 1.73 Hz, 1H), 7.71-7.65 (m, 2H), 7.53 (d, J=9.08Hz, 1H), 7.33 (dt,
25

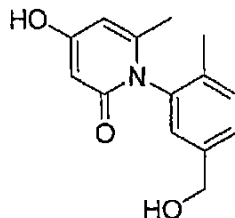
$J=9.95$, 2.59 Hz, $1H$), 7.17 (dt, $J=8.22$, 2.59 Hz, $1H$), 6.68 (s, $1H$), 5.32 (s, $2H$), 1.89 (s, $3H$). ES-MS m/z 481.9585 ($M-H$ calcd for $C_{20}H_{12}BrClF_2NO_4$, requires 481.9601).

5 Example 481



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

10 Step 1: Preparation of 4-hydroxy-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl pyridin-2(1H)-one .

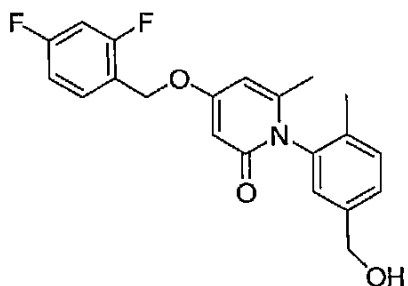


15 4-Hydroxy-6-methyl-2-pyrone (23.0 g, 182.2 mmol) and 3-Amino-4-methylbenzyl alcohol (25.0 g, 182.2 mmol) were taken up in 25 ml of 1,2-dichlorobenzene. The solution was heated to $165^{\circ}C$ in a 250 ml round bottom flask equipped with a J-Kem temperature controller probe, and a heating mantle. In a
20 separate 250 ml round bottom flask 4-Hydroxy-6-methyl-2-pyrone (23.0 g, 182.2 mmol) was suspended in 25 ml of 1,2-dichlorobenzene and also heated to $165^{\circ}C$. The pyrone solution was poured into the flask containing the aniline and the reaction stirred at $165^{\circ}C$ for 20 minutes. The reaction was
25 allowed to cool to room temperature. Reaction contents were

washed with saturated NaHCO_3 (aq.). Separated the organic and aqueous layers. Aqueous layer was made acidic with dropwise addition of concentrated HCl . The product was extracted from the acidic aqueous layer with $n\text{-BuOH}$. $n\text{-BuOH}$ removed in vacuo to produce a reddish brown oil. (8.5 g, 19%). Contents carried forward to next reaction with no further purification.

^1H NMR (300 MHz, CD_3OD) δ 7.35 (m, 2H), 7.08 (s, 1H), 6.08 (br s, 1H), 5.81 (br s, 1H), 4.60 (s, 2H), 2.01 (s, 3H), 1.87 (s, 3H). LC/MS, t_r = 1.42 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 246.1131 ($\text{M}+\text{H}$). ES-HRMS m/z 246.1107 ($\text{M}+\text{H}$ calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_3$ requires 246.1125).

Step 2: 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one .

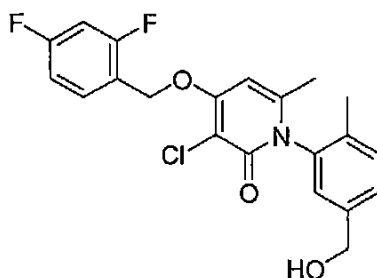


4-hydroxy-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl pyridin-2(1H)-one (from Step 1) (8.0 g, 32.6 mmol) was stirred briskly at room temperature with 2,4-difluorobenzyl bromide (4.2 ml, 32.6 mmol) and K_2CO_3 (4.5 g, 32.6 mmol) in 50 ml of dimethylformamide. After stirring for 8 hours, H_2O (100 ml) was added to reaction mixture. The product was extracted with ethyl acetate. Ethyl acetate layer was separated and dried over Na_2SO_4 . Ethyl acetate was removed in vacuo. A yellow oil was obtained. The oil was passed through a plug of silica gel first eluting with 500 ml of ethyl acetate/hexane

(1:1). This eluent was set aside. Next, ethyl acetate (100%) was passed through the plug until desired product was completely flushed from silica (3 liters). Solvent was removed in vacuo. Light yellow oil obtained (7.5 g, 62%). ¹H NMR (300 MHz, CD₃OD) δ 7.60 (app q, J = 6.44 Hz, 1H), 7.42 (d, J = .81 Hz, 2H), 7.15 (s, 1H), 7.06 (m, 2H), 6.21 (dd, J = 1.61, 1.00 Hz, 1H), 6.12 (d, J = 2.62 Hz, 1H), 5.16 (s, 2H), 4.65 (s, 2H), 2.07 (s, 3H), 1.93 (s, 3H); LC/MS, t_r = 2.38 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 372 (M+H).

Step 3: Preparation of the title compound . 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methyl-pyridin-2(1H)-one (from Step 2) (4.0 g, 10.8 mmol) was stirred at room temperature with N-bromosuccinimide (2.1 g, 11.9 mmol) in 100 ml of CH₂Cl₂ for 2.0 hours. The reaction was evaporated on a rotary evaporator and the resulting solid was washed with acetonitrile and dried in vacuo to yield a white solid (3.9 g, 80%). ¹H NMR (300 MHz, CDCl₃) δ 7.67 (app q, J = 6.24 Hz, 1H), 7.35 (d, J = 1.01 Hz, 2H), 7.10 (s, 1H), 7.04 (m, 1H), 6.91 (ddd, J = 11.08, 8.66, 2.42 Hz, 1H), 6.15 (d, J = 0.63 Hz, 2H), 5.29 (s, 2H), 4.66 (s, 2H), 2.08 (s, 3H), 1.97 (s, 3H); ES-MS m/z 450 (M+H). ES-HRMS m/z 450.0467 (M+H calcd for C₂₁H₁₉BrF₂NO₃ requires 450.0511).

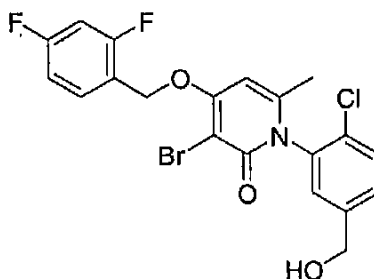
Example 482



3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

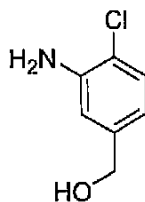
5 The title compound was prepared by a procedure similar to the one described for Example 481, except that the product from Step 2, Example 481 was chlorinated instead of being brominated. The procedure is as follows: 4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one (from Step 2, Example 481 above) (7.0 g, 18.8 mmol) was refluxed with N-chlorosuccinimide (2.5 g, 18.8 mmol) in 50 ml of CH₂Cl₂ overnight. The reaction was evaporated on a rotary evaporator and the resulting solid was stirred in MeOH. The precipitate was collected on a filter
10 pad, washed with MeOH and dried in vacuo to yield a white solid (1.6 g, 21%). ¹H NMR (300 MHz, DMF-d₇) δ 7.85 (app q, J = 6.44 Hz, 1H), 7.43 (d, J = 0.81, 1H), 7.42 - 7.23 (m, 3H), 6.84 (s, 1H), 5.48 (s, 2H), 4.67 (s, 2H), 2.05 (s, 3H), 2.03 (s, 3H); ES-MS m/z 406 (M+H). ES-HRMS m/z 406.1033 (M+H calcd
15 for C₂₁H₁₆ClF₂NO₄ requires 406.1016).

Example 483



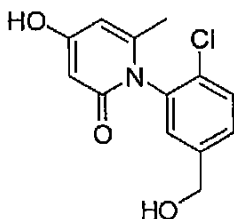
25 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

Step 1: Preparation of 3-amino-4-chloro-benzyl alcohol.



3-Nitro-4-chloro-benzyl alcohol (23.0 g, 122.6 mmol) is taken up in isopropyl alcohol (175 ml) and water (35 ml). Iron powder (<10 micron) (68.0 g, 1.2 moles) and NH_4Cl (66.0 g, 1.2 moles) are added. The suspension is stirred overhead at 70°C in a three neck round bottom flask equipped with a heating mantle and a J-Kem temperature controller probe. After 4 hours, isopropyl alcohol was removed in vacuo. Water (100 ml) and concentrated HCl (10 ml) was added to mixture. Contents are transferred to a separatory funnel and ethyl acetate is used to extract the aqueous layer of impurities. The aqueous layer was then basified with 50% aqueous NaOH. The product was extracted from the basic aqueous layer with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 and then removed in vacuo. The remaining residue was taken up in 50% ethyl acetate/hexane and the precipitate was collected on a filter pad. Precipitate was washed with 50% ethyl acetate/hexane to yield a flocculent brown solid (8.4 g, 44%). ^1H NMR (300 MHz, CD_3OD) δ 7.17 (d, J = 8.26 Hz, 1H), 6.86 (d, J = 2.01 Hz, 1H), 6.66 (dd, J = 2.01, 0.61 Hz, 1H), 4.51 (s, 2H); LC/MS, t_r = 0.32 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C); ES-MS m/z 158 ($\text{M}+\text{H}$).

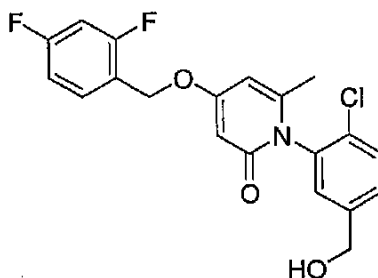
Step 2: 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one .



3-amino-4-chloro-benzyl alcohol (8.0g, 51.0 mmol) and 4-hydroxy-6-methyl-2-pyrone (6.4 g, 51.0mmol) were taken up in 1,2-dichlorobenzene (50 ml). The mixture was plunged into a 165°C oil bath where it stirred for 20 minutes. The reaction
5 was cooled to room temperature and the reaction was worked up by washing with saturated NaHCO₃ (aq.) and extracting impurities with ethyl acetate. The product remained in the aqueous layer. The basic aqueous layer was made acidic with concentrated HCl. The product was extracted from the acidic
10 aqueous layer with ethyl acetate. The ethyl acetate layer was dried over Na₂SO₄ and the solvent removed in vacuo. The product was obtained as a yellow oil in a 26% yield and was carried through to the next step with no further purification.
¹H NMR (300 MHz, CD₃OD) δ 7.62 (d, J = 8.26 Hz, 2H), 7.51 (dd, J = 8.46, 2.22 Hz, 1H), 7.36 (d, J = 2.01 Hz, 1H), 6.13 (br s, 1H), 5.84 (d, J = 2.42 Hz, 1H), 4.68 (s, 2H), 1.97 (s, 3H);
LC/MS, t_r = 0.25 minutes and 1.41 minutes (tautomer), (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 266 (M+H).

20

Step 3: 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxyl]-6-methylpyridin-2(1H)-one .

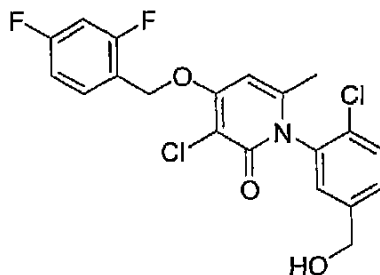


1-[2-chloro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one (from step 2) (3.5g, 13.2 mmol) was
25 taken up in DMF (10 ml) and cooled to 0°C. 2,4-Difluorobenzyl bromide (1.7 ml, 13.2 mmol) and K₂CO₃ (1.8 g, 13.2 mmol) were added and the reaction stirred for 6 hours. The reaction was

worked up by adding saturated NaHCO_3 (aq.) and extracting with ethyl acetate. The ethyl acetate extraction was washed with water, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and dried over Na_2SO_4 ,
5 filtered, and the solvent removed in vacuo. The product was obtained in 83% crude yield and carried through to the next step as a brown oil. LC/MS, t_r = 2.48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 392 ($M+H$). ES-HRMS m/z 392.0853
10 ($M+H$ calcd for $\text{C}_{20}\text{H}_{17}\text{ClF}_2\text{NO}_3$ requires 392.0860).

Step 4: The title compound was prepared from 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (from step 3) (1.8g, 4.6 mmol) and N-bromosuccinimide (0.82 g, 4.6 mmol) by dissolving them in
15 CH_2Cl_2 (10 ml) and stirring for 2 hours at room temperature. The solvent was removed in vacuo and the residue was taken up in CH_3CN . The precipitate was collected on a filter pad and rinsed with CH_3CN to yield a white solid (370 mg, 17%). ^1H
20 NMR (300 MHz, CDCl_3) δ 7.65 (app q, J = 6.24 Hz, 1H), 7.52 (d, J = 8.26 Hz, 1H), 7.40 (dd, J = 8.26, 2.01 Hz 1H), 7.26 (d, J = 0.81 Hz, 1H), 7.03 (m, 1H), 6.91 (ddd, J = 11.08, 8.66, 2.42 Hz, 1H), 6.17 (d, J = 0.81 1H), 5.29 (s, 2H), 4.63 (s, 2H), 2.02 (s, 3H); ES-MS m/z 471 ($M+H$). ES-HRMS m/z 471.9953 ($M+H$)
25 calcd for $\text{C}_{20}\text{H}_{16}\text{BrClF}_2\text{NO}_3$ requires 471.9944).

Example 484

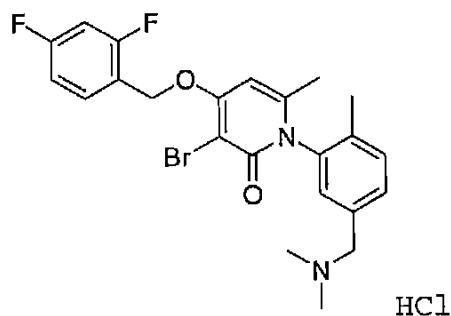


3-chloro-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

The title compound was prepared from 1-[2-chloro-5-(hydroxymethyl)phenyl]-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (2.4 g, 6.1 mmol) and NCS (815.0 mg, 6.1 mmol) in 65°C dichloroethane (20 ml). A catalytic amount of dichloroacetic acid (2 drops) was added. After two hours the solvent was removed in vacuo and the residue was taken up in diethyl ether. The precipitate was collected on a filter pad and then taken up in 50% ethyl acetate/hexanes to remove residual succinimide. The precipitate was collected on a filter pad and then dried in vacuo to produce a white powder (180 mg, 6.9%). ¹H NMR (300 MHz, CDCl₃) δ 7.61 (app q, J = 6.44 Hz, 1H), 7.52 (d, J = 8.26 Hz, 1H), 7.40 (dd, J = 8.26, 2.01 Hz, 1H), 7.27 (d, J = 2.01 Hz, 1H), 7.00 (m, 1H), 6.91 (m, 1H), 6.20 (s, 1H), 5.29 (s, 2H), 4.65 (s, 2H), 2.03 (s, 3H); ES-MS m/z 426 (M+H). ES-HRMS m/z 426.0453 (M+H calcd for C₂₀H₁₆Cl₂F₂NO₃ requires 426.0470).

20

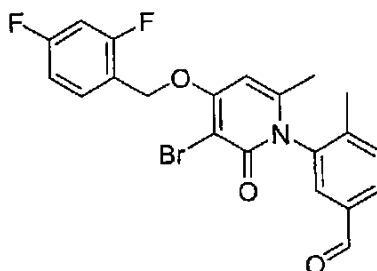
Example 485



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-(dimethylamino)methyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one hydrochloride

25

Step 1: Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzaldehyde.

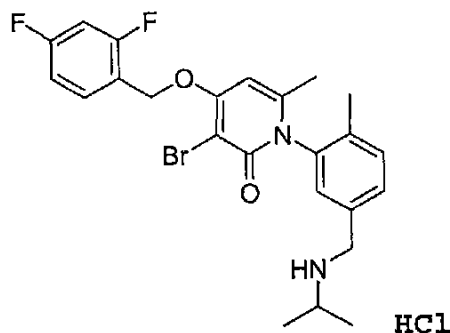


5 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(hydroxymethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one (1.5g, 3.33 mmol) was dissolved in 75% CH₃CN/CH₂Cl₂ (20ml) and cooled to 0°C. Dess-Martin Periodinane (2.8 g, 6.66 mmol) was added and the reaction stirred for four hours. At this time, the reaction
10 was quenched with 5% sodium bisulfite (aq.). The product was extracted with ethyl acetate. The combined organic extracts were then washed with saturated NaHCO₃ (aq.). The aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated.
15 The resulting residue was taken up in diethyl ether and the precipitate was collected on a filter pad and washed with more diethyl ether to yield a white solid (1.35 g, 91%). ¹H NMR (300 MHz, CDCl₃) δ 10.00 (s, 1H), 7.91 (dd, J = 7.65, 1.61 Hz, 1H), 7.65 (m, 2H), 7.57 (d, J = 7.85 Hz, 1H), 7.03 (m, 1H),
20 6.95 (ddd, J = 12.69, 8.86, 2.62 Hz, 1H), 6.19 (s, 1H), 5.31 (s, 2H), 2.20 (s, 3H), 1.96 (s, 3H); ES-MS m/z 448 (M+H). ES-HRMS m/z 448.0347 (M+H calcd for C₂₁H₁₇BrF₂NO₃ requires 448.0354).

25 Step 2: Preparation of the title compound. 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzaldehyde (from step 1) (0.50 g, 1.11 mmol) was dissolved in CH₂Cl₂ (10 ml). N,N-dimethylamine (2.0 M in THF)

(1.11 ml, 2.22 mmol) was added. This mixture stirred for at room temperature for 12 hours. Next, sodium tri-acetoxyborohydride (0.47 g, 2.22 mmol) was added and the reaction stirred for two more hours. The reaction was washed
5 with 1 N NaOH (aq.) and then extracted with CH₂Cl₂. The combined organic extracts were washed with water. The aqueous layer was separated and extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was taken up in
10 diethyl ether. 1M HCl in diethyl ether (5 ml) was added and the precipitate was collected on a filter pad. This precipitate was hygroscopic. The hygroscopic solid was then taken up in hot ethyl acetate. Hexane was added until a precipitate crashed out. The precipitate was collected on a
15 filter pad to yield a white solid (150 mg, 26%). ¹H NMR (400 MHz, D₂O) δ 7.42 (m, 3H), 7.17 (s, 1H), 6.86 (m, 2H), 6.53 (s, 1H), 5.20 (s, 2H), 4.18 (s, 1H), 2.72 (s, 6H), 1.85 (s, 3H), 1.82 (s, 3H); ES-MS m/z 477 (M+H). ES-HRMS m/z 477.0955 (M+H calcd for C₂₃H₂₄BrF₂N₂O₂ requires 477.0984).

20



Example 486

3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-[(isopropylamino)methyl]-2-methylphenyl)-6-methylpyridin-2(1H)-one hydrochloride

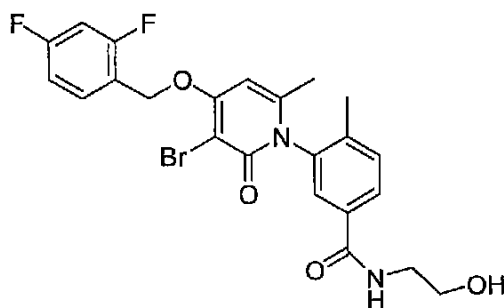
25

The title compound was prepared by reductive amination of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-

1 (2H)-yl]-4-methylbenzaldehyde (from step 1) (0.50 g, 1.11 mmol) with iso-propyl amine (0.13 g, 2.22) according to the procedure described above for Example 485 (Step 2) to give the desired compound (0.49g, 84%). ¹H NMR (400 MHz, CD₃OD) δ 7.64 (app quartet, J = 6.58 Hz, 1H), 7.53 (m, 2H), 7.29 (br s, 1H), 7.03 (m, 1H), 6.68 (s, 1H), 5.36 (s, 2H), 4.22 (s, 2H), 3.46 (m, 1H), 2.06 (s, 3H), 2.01 (s, 3H), 1.37 (d, J = 6.58 Hz, 6H) ; ES-MS m/z 491 (M+H). ES-HRMS m/z 491.1107 (M+H calcd for C₂₄H₂₆BrF₂N₂O₂ requires 491.1140).

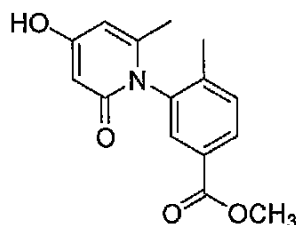
10

Example 487



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N-(2-hydroxyethyl)-4-methylbenzamide

15



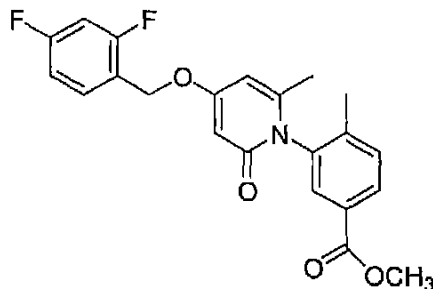
Step 1: Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate .

20

4-Hydroxy-6-methyl-2-pyrone (22.9 g, 181.6 mmol) and methyl-3-amino-2-methylbenzoate (25 g, 151.3 mmol) were suspended in 50 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle.

The reaction was heated to 165°C for 15 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 110°C. At this point, 200 ml of toluene was added. The flask was
5 plunged into a 0°C ice bath while stirring. "Oiling out" occurred. Perhaps too much toluene was added so some of the solvent was removed in vacuo. The oil went back into solution and a light brown precipitate remained. The toluene mixture was allowed to stir for 72 hours at room temperature. A
10 precipitate was collected on a filter pad. The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C. water to remove excess pyrone, and dried in vacuo to give a tan solid (16.5 g, 40% yield). ¹H NMR (300 MHz, CD₃OD) δ 8.06 (dd, J = 8.06, 1.61 Hz, 1H), 7.80 (d, J = 1.61 Hz, 1H),
15 7.56 (d, J = 8.06, Hz, 1H), 6.15 (dd, J = 2.42, 0.81 Hz, 1H), 5.86 (d, J = 2.42 1H), 3.94 (s, 3H), 2.15 (s, 3H), 1.91 (s, 3H); ES-MS m/z 274 (M+H). ES-HRMS m/z 274.1066 (M+H calcd for C₁₅H₁₆NO₄ requires 274.1074).

20 Step 2: Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate .



Methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methylbenzoate (from Step 1) (16.5 g, 60.4 mmol) 2,4-difluorobenzyl bromide (7.8 ml, 60.4 mmol) were taken up in
25 250 ml of N,N-dimethylformamide and the mixture was cooled to 0°C. K₂CO₃ (8.3g, 60.4 mmol) was added and reaction stirred for 12 hours during which time the reaction was allowed to

warm to room temperature. LC/MS indicated the presence of starting material after 12 hours. An excess of K_2CO_3 was added at room temperature along with 0.50 ml of 2,4-difluorobenzyl bromide. The reaction stirred for an additional two hours.

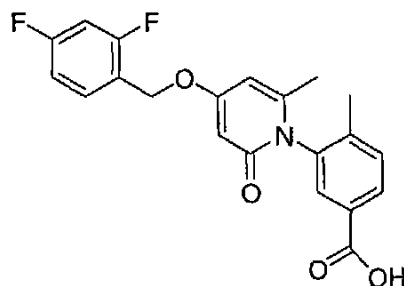
5 Saturated $NaHCO_3$ (aq.) was poured into reaction vessel. The solution was extracted with ethyl acetate and the organic layers were combined then washed with water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and dried

10 over Na_2SO_4 , and evaporated. The product was carried on to the next step as a crude oil (24.1 g, quantitative yield). 1H NMR (300 MHz, $CDCl_3$) δ 8.06 (dd, $J = 7.85, 1.61$ Hz, 1H), 7.82 (d, $J = 1.61$, 1H), 7.52-7.44 (m, 2H), 7.01 - 6.88 (m, 2H), 6.05 (d, $J = 2.62$ Hz, 1H), 5.97 (dd, $J = 2.62, 0.81$ Hz, 1H), 5.08 (s,

15 2H), 3.93 (s, 3H), 2.20 (s, 3H), 1.89 (s, 3H); ES-MS m/z 400 (M+H). ES-HRMS m/z 400.1374 (M+H calcd for $C_{22}H_{20}F_2NO_4$ requires 400.1355).

Step 3: Preparation of 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .

20

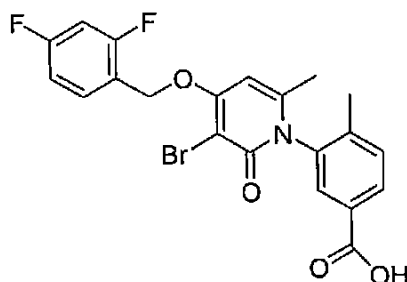


Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (14g, 35.0 mmol) (from step 2) was taken up in THF (25 ml) and H_2O . 2.5 N $NaOH$ (aq.)

25 was added and the reaction stirred for 30 minutes at room temperature. The reaction was made acidic via the addition of concentrated HCl . The product was extracted with ethyl acetate. The ethyl acetate extraction was dried over Na_2SO_4 ,

filtered, and the solvent removed in vacuo. Upon vacuum removal of the solvent, the product crashed out of the ethyl acetate. This precipitate was collected on a filter pad and washed with a 50 ethyl acetate/hexanes to yield a white powder
 5 (9g, 7%). ¹H NMR (300 MHz, CDCl₃) δ 8.01 (dd, J = , 1.61 Hz, 1H), 7.84 (d, J = 1.61 Hz, 1H), 7.52 - 7.47 (app q, J = 8.26, 1H), 7.43 (d, J = 8.06 Hz, 1H), 7.00 - 6.88 (m, 2H), 6.19 (d, J = 2.62 Hz, 1H), 6.05 (dd, J = 2.62, 1.81 Hz, 1H), 5.17 (s, 2H), 2.19 (s, 3H), 1.90 (s, 3H); ES-HR/MS m/z 386.12 (M+H
 10 calcd for C₂₁H₁₈F₂NO₄ requires 386.1198).

Step 4: Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .



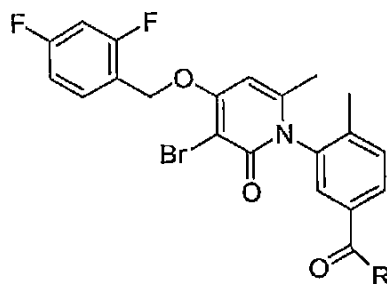
15

3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (5.9 g, 15.2 mmol) (from step 3 above) was taken up in dichloromethane (25 ml). N-Bromosuccinimide was added and the reaction stirred for 14
 20 hours. The dichloromethane was removed in vacuo and the residue was taken up in acetonitrile. The precipitate was collected on a filter pad and rinsed with acetonitrile to yield the desired product as a white solid (5.2 g, 74%). ¹H
 25 NMR (300 MHz, CD₃OD) δ 7.87 (dd, J = 7.85, 1.61, Hz, 1H), 7.82 (d, J = 1.81 Hz, 1H), 7.69 (app q, J = 8.06 Hz 1H), 7.57 (d, J = 8.06 Hz, 1H), 7.09 (dt, J = 8.66, 2.22 Hz, 1H), 6.70 (s, 1H), 5.40 (s, 2H), 2.14 (s, 3H), 2.02 (s, 3H); ES-MS m/z 464

(M+H). ES-HRMS m/z 464.0275 (M+H calcd for $C_{21}H_{17}BrF_2NO_4$ requires 464.0304).

Step 5: Preparation of the title compound. 3-[3-bromo-4-
5 [(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from Step 4 above) (1.9g, 4.10 mmol) was dissolved in 20 ml of CH_2Cl_2 . Ethanolamine (297 μ l, 4.92 mmol) was added, followed, in order, by EDCI (0.764 g, 4.92 mmol), 1-hydroxybenzotriazole (0.665g, 4.92 mmol) and triethylamine
10 (1.14 ml, 8.20 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl and extracted 3 times with ethyl acetate. The combined organic layer was then washed with saturated $NaHCO_3$ (aq.) and extracted 3 times with ethyl acetate. The organic layers were
15 combined and washed with H_2O and extracted 3 times with ethyl acetate. The organic layers were combined and dried over Na_2SO_4 and evaporated. The resulting residue was triturated with diethyl ether/hexane to obtain a solid, which was dried in vacuo to give a white solid (1.5g, 72%). 1H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.85, 1.61 Hz, 1H), 7.65 (d, J = 1.61 Hz, 1H), 7.62 (app q, J = 8.26 Hz, 1H), 7.40 (d, J = 8.06 Hz, 1H), 7.39 - 7.30 (m, 1H), 7.03 - 6.97 (m, 1H), 6.88 - 6.81 (m, 1H), 6.25 (s, 1H), 5.20 (s, 2H), 3.70 - 3.52 (m, 1H), 3.16 - 3.12 (m, 2H), 2.10 (s, 3H), 1.98 (s, 3H); ES-MS m/z 507
20 (M+H). ES-HRMS m/z 507.0719 (M+H calcd for $C_{23}H_{22}BrF_2N_2O_4$ requires 507.0726).

Examples 488-491

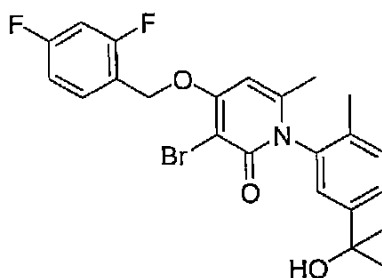


The compounds of Examples 488-491-476 are prepared essentially according to the procedures set forth for Example 487.

5

Compound No.	R	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 488	-NH(CH ₂) ₂ OCH ₃	84	C ₂₄ H ₂₄ BrF ₂ N ₂ O ₄	528.0882	521.0868
Ex. 489	-NHCH ₃	79	C ₂₂ H ₂₀ BrF ₂ N ₂ O ₃	477.0620	477.0602
Ex. 490	-N(CH ₃) ₂	54	C ₂₃ H ₂₂ BrF ₂ N ₂ O ₃	491.0776	491.0753
Ex. 491	-morpholine	65	C ₂₅ H ₂₄ BrF ₂ N ₂ O ₄	533.0858	533.0882

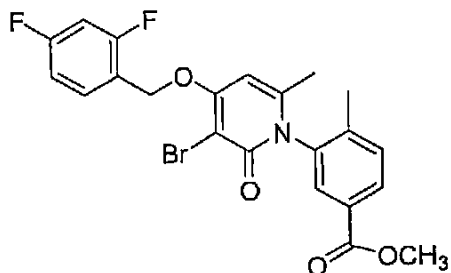
Example 492



10 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[5-(1-hydroxy-1-methylethyl)-2-methylphenyl]-6-methylpyridin-2(1H)-one

Step 1: Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate .

15



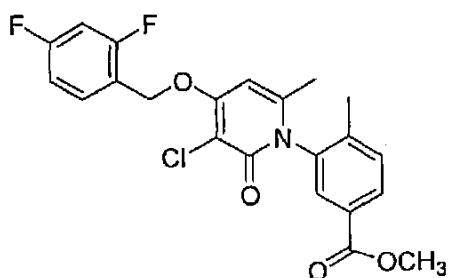
Methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (as prepared above) (1.8g, 4.51 mmol) was taken up in CH₂Cl₂ (10 ml). N-bromosuccinimide (0.80 g, 4.51 mmol) was added and the mixture stirred at room temperature for two hours. The CH₂Cl₂ is removed in vacuo and the residue is taken up in CH₃CN. The resulting precipitate is collected on a filter pad and washed with CH₃CN to yield a white solid (0.30 g, 14%, first crop).

¹H NMR (300 MHz, CDCl₃) δ 8.06 (dd, J = 8.06, 1.61 Hz, 1H), 7.80 (d, J = 1.61 Hz, 2H), 7.65 (app q, J = 8.46 Hz, 1H), 7.48 (d, J = 8.06, 1H), 7.05 - 6.99 (m, 1H), 6.96 - 6.89 (m, 1H), 6.16 (s, 1H), 5.31 (s, 2H), 3.93 (s, 3H), 2.17 (s, 3H), 1.96 (s, 3H). ES-HRMS m/z 478.0476 (M+H calcd for C₂₂H₁₉BrF₂NO₄ requires 478.0476).

Step 2: Preparation of the title compound. Methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (0.22 g, 0.46 mmol) was taken up in THF and cooled to 0°C. MeMgCl (3.0 M in THF) (0.73 ml, 2.2 mmol) was slowly added to the 0°C solution. The reaction was allowed to proceed without maintaining the 0°C bath temperature. The reaction was complete within two hours. At this time the mixture was quenched with saturated NH₄Cl (aq.) and extracted with ethyl acetate. The organic layers were combined, washed with H₂O, and extracted with ethyl acetate. The organic layers were combined and dried over Na₂SO₄, filtered, and evaporated. The residue was taken up in 50% ethyl acetate/hexanes. The

precipitate was collected on a filter pad and washed with 50% ethyl acetate/hexanes to yield a white solid (0.10 g, 45%).
¹H NMR (300 MHz, CD₃OD) δ 7.70 (app q, J = 8.26, Hz, 1H), 7.54 (dd, J = 8.06, 2.01 Hz, 1H), 7.40 (d, J = 1.81 Hz, 1H), 7.12 - 7.06 (m, 2H), 6.68 (s, 1H), 5.40 (s, 2H), 2.05 (s, 3H), 2.02 (s, 3H), 1.57 (s, 6H). ES-HRMS m/z 478.0785 (M+H calcd for C₂₃H₂₃BrF₂NO₃ requires 478.0824).

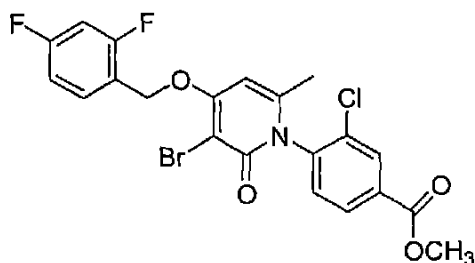
Example 493



methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate

The title compound was prepared by taking up methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoate (1.46g, 3.66 mmol) in dichloroethane (25 ml) and adding N-chlorosuccinimide (0.49g, 3.66 mmol), dichloroacetic acid (catalytic), and heating to 50°C for 6 hours. At this time, the solvent was removed in vacuo and the residue taken up in diethyl ether. The precipitate was collected on a filter pad. ¹H NMR (300 MHz, CDCl₃) δ 8.07 (dd, J = 7.85, 1.61 Hz, 1H), 7.80 (d, J = 1.81 Hz, 2H), 7.62 (app q, J = 8.46 Hz, 1H), 7.48 (d, J = 7.85, 1H), 7.05 - 6.95 (m, 1H), 6.93 - 6.89 (m, 1H), 6.19 (s, 1H), 5.30 (s, 2H), 3.93 (s, 3H), 2.17 (s, 3H), 1.97 (s, 3H). ES-HRMS m/z 434.0932 (M+H calcd for C₂₂H₁₉ClF₂NO₄ requires 434.0965).

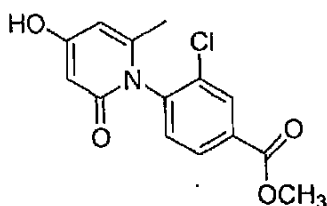
Example 494



methyl 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate

5

Step 1: Preparation of methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate .



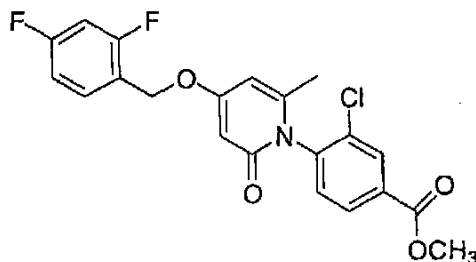
10

4-Hydroxy-6-methyl-2-pyrone (24.5 g, 193.9 mmol) and methyl-3-amino-2-chlorobenzoate (30 g, 161.6 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 175°C for 20 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 110°C. At this point, 200 ml of toluene was added. The toluene mixture was allowed to stir for 72 hours at room temperature. A precipitate was collected on a filter pad. The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C. water to remove excess pyrone, and dried in vacuo to give a tan solid (13.0 g, 27% yield). ¹H NMR (300 MHz, CD₃OD) δ 8.26 (d, J = 1.81 Hz, 1H), 8.14 (dd, J = 8.26, 1.81 Hz, 1H),

7.54 (d, $J = 8.26$, Hz, 1H), 6.14(dd, $J = 2.42$, 1.0 Hz, 1H), 5.83 (d, $J = 2.42$ 1H), 4.00 (s, 3H), 1.96 (s, 3H); LC/MS, $t_r = 1.81$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 (M+H).

5

Step 2: Preparation of methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .



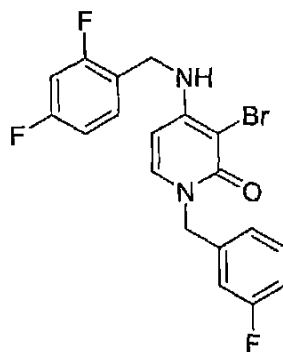
Methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (from Step 1) (2.4g, 8.17 mmol) was taken up in DMF (10 ml). 2,4-difluorobenzylbromide (1.05 ml, 8.17 mmol) and K_2CO_3 (1.13 g, 8.17 mmol) were added. The reaction stirred for 6 hours at room temperature. At this time, the reaction was poured into water (200 ml) and extracted with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 , filtered, and the solvent removed in vacuo to give amber oil (2.62 g, 77% crude yield). LC/MS, $t_r = 2.79$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 (M+H).

20

Step 3: Preparation of the title compound . Methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 2) (2.60g, 6.21 mmol) was taken up in CH_2Cl_2 (20 ml). N-bromosuccinimide (1.11g, 6.21 mmol) was added and the mixture stirred at room temperature for 4 hours. The CH_2Cl_2 is removed in vacuo and the residue is taken up in CH_3CN . The resulting precipitate is collected on a filter pad and washed with CH_3CN to yield a white solid (0.75 g, 24%). 1H

NMR (300 MHz, CDCl₃) δ 8.22 (d, J = 1.88 Hz, 1H), 8.06 (dd, J = 8.19, 1.75 Hz, 1H), 7.59 (app q, J = 8.46 Hz, 1H), 7.33 (d, J = 8.19, 1H), 6.96 (dt, J = 8.06, 1.21 Hz, 1H), 6.89 – 6.84 (m, 1H), 6.13 (s, 1H), 5.26 (s, 2H), 3.95 (s, 3H), 1.95 (s, 3H). ES-HRMS m/z 497.9892 (M+H calcd for C₂₂H₁₆BrClF₂NO₄ requires 497.9914).

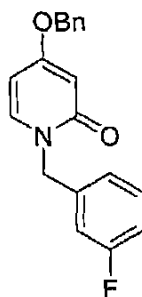
Example 495



10 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one

Step 1

Preparation of 4-(benzyloxy)-1-(3-fluorobenzyl)pyridin-2(1H)-one
15 one

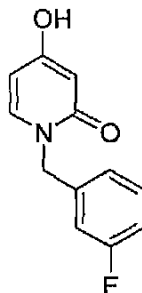


A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 4-benzyloxy-2(1H)-pyridinone (20 g, 99.6 mmol) and N,N-dimethyl formamide (50 mL). K₂CO₃ (13.7 g, 99.6 mmol) and KI (1.6 g, 9.6 mmol) were added
20 followed by 3-fluorobenzyl bromide (14.6 mL, 119.4 mmol). The reaction mixture was heated for 18 h at 80 C. The reaction

mixture was concentrated in vacuo and treated with hot ethyl acetate. The solids were filtered off, the filtrate was poured into water and was extracted with ethyl acetate. The organic extract was washed with brine, dried with anhydrous Na₂SO₄, and concentrated in vacuo. The residue was dissolved in hot ethyl acetate and precipitated with hexanes to give the title compound (10 g, 33%). ¹H NMR (400 MHz, CD₃OD) δ 7.57 (d, J = 8.4 Hz, 1H), 7.37 (m, 5H), 7.07 (d, J = 8.4 Hz, 1H), 7.01 (app d, J = 8.4 Hz, 2H), 6.17 (d, J = 2.68 and 7.6 Hz, 1H), 6.04 (d, J = 2.68 Hz, 1H), 5.10 (s, 2H), 5.08 (s, 2H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -114.88 (1 F) ppm. ES-HRMS m/z 310.1271 (M+H calcd for C₁₉H₁₇FNO₂ requires 310.1238).

Step 2

15 Preparation of 1-(3-fluorobenzyl)-4-hydroxypyridin-2(1H)-one

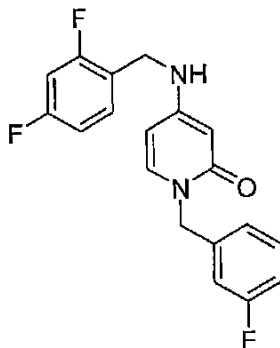


A small Parr bottle was charged with SC-82484 (10 g, 32.3 mmol), ethanol (175 mL) and 10% Pd/C (0.5 g). The system was flushed twice with both nitrogen and hydrogen. The reaction mixture was hydrogenated at 30 psi until no starting material was visible by LC-MS. The reaction mixture was slurried with Celite and then was filtered through a pad of celite. The filtrate and ensuing ethanol washes were concentrated in vacuo to give a beige solid. ¹H NMR (400 MHz, CD₃OD) δ 7.53 (d, J = 7.67 Hz, 1H), 7.32 (m, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.05 (dd, J = 2.58 and 7.67 Hz, 1H), 5.83 (d,

$J = 2.0$ Hz, 2H), 5.10 (s, 2H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -115.33 (1 F) ppm. ES-HRMS m/z 218.0641 ($M+H$ calcd for $\text{C}_{12}\text{H}_{11}\text{FNO}_2$ requires 218.0612).

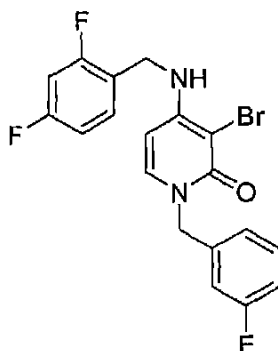
5 Step 3

Preparation of 4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one



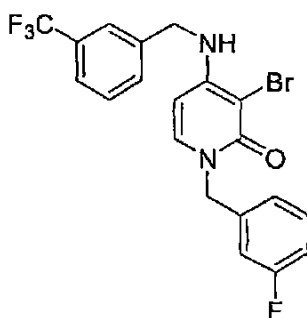
The product from Step 2 (0.5 g, 2.28 mmol) and 2,4-difluoro benzylamine (4 mL, 33.6 mmol) were combined in a nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was chromatographed on silica (95:5 ethyl acetate: methanol). The final compound was isolated as a light yellow solid (0.16 g, 36%). ^1H NMR (400 MHz, CD_3OD) δ 7.33 (m, 3H), 7.03 (d, $J = 8$ Hz, 1H), 6.96 (m, 3H), 6.95 (m, 1H), 5.97 (dd, $J = 3.2$ and 8.0 Hz, 1 H), 5.48 (d, $J = 2.56$ Hz, 1H), 5.02 (s, 2H), 4.33 (s, 2H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -113.88 (1 F), -115.33 (1F), -116.78 (1F) ppm. ES-HRMS m/z 345.1221 ($M+H$ calcd for $\text{C}_{19}\text{H}_{17}\text{F}_3\text{N}_2\text{O}$ requires 345.1209).

Step 4 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(3-fluorobenzyl)pyridin-2(1H)-one



N-Bromo succinimide (81 mg, 0.46 mmol) was added to a solution of the product from Step 3 (0.15 g, 0.44 mmol) in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction was complete by LC-MS. The reaction mixture was poured into saturated aqueous NaHCO₃. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous MgSO₄, and concentrated in vacuo. ¹H NMR (400 MHz, CDCl₃) δ 7.3-7.2 (m, 4H), 7.07 (app t, J = 7.6 Hz, 2H), 6.97 (m, 2H), 6.80 (m, 2H), 5.78 (d, J = 7.6 Hz, 1H), 5.30 (br s, 1H), 5.08 (s, 2H), 4.46 (d, J = 6 Hz, 2H) ppm. ¹⁹F NMR (400 MHz, CDCl₃) δ -110.64 (1 F), -112.75 (1F), -114.79 (1F) ppm. ES-HRMS m/z 423.0275 (M+H calcd for C₁₉H₁₅BrF₃N₂O requires 423.0314).

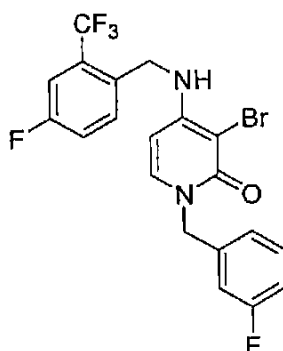
Example 496



3-bromo-1-((3-fluorobenzyl)amino)-4-((3-(trifluoromethyl)benzyl)amino)pyridin-2(1H)-one

The title compound was prepared essentially as in Example 495. ^1H NMR (400 MHz, CDCl_3) δ 7.54 (m, 2H), 7.48 (m, 2H), 7.27 (q, $J = 3.1, 9.0$ Hz, 1H), 6.96 (app t, $J = 8.8$ Hz, 2H), 5.71 (d, $J = 7.6$ Hz, 1H), 5.4 (br m, 1H), 5.08 (s, 2H), 4.52 (d, $J = 5.6$ Hz, 2H) ppm. ^{19}F NMR (400 MHz, CDCl_3) δ -63 (3 F), -112 (1 F) ppm. ES-HRMS m/z 455.0388 ($M+H$ calcd for $\text{C}_{20}\text{H}_{16}\text{BrF}_4\text{N}_2\text{O}$ requires 455.0377).

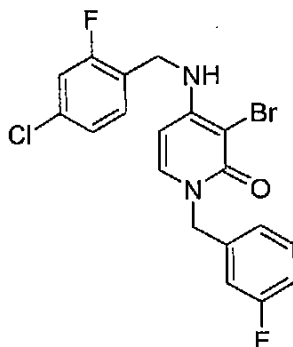
Example 497



3-bromo-1-(3-fluorobenzyl)-4-{[4-fluoro-2-(trifluoromethyl)benzyl]amino}pyridin-2(1H)-one

The title compound was prepared essentially as in Example 495. ^1H NMR (400 MHz, CDCl_3) δ 7.43 (m, 2H), 7.27 (m, 3H), 7.07 (m, 2H), 6.99 (m, 2H), 5.65 (d, $J = 10$ Hz, 1H), 5.46 (br s, 1H), 5.09 (s, 2H), 4.64 (s, 2H) ppm. ^{19}F NMR (400 MHz, CDCl_3) δ -61.31 (3 F), -112.69 (1 F), 112.97 (1F) ppm. ES-HRMS m/z 473.0246 ($M+H$ calcd for $\text{C}_{20}\text{H}_{15}\text{BrF}_5\text{N}_2\text{O}$ requires 473.0282).

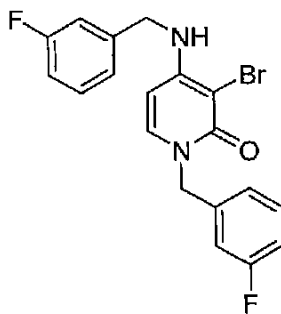
Example 498



Preparation of 4-bromo-1-((4-chloro-2-fluorobenzyl)amino)-1-(3-fluorobenzyl)pyridin-2(1H)-one

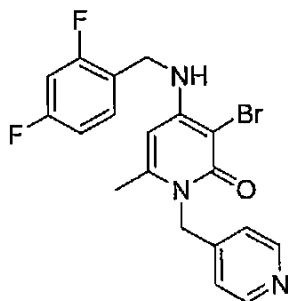
- 5 The title compound was prepared essentially as in Example 495. ^1H NMR (400 MHz, CDCl_3) δ 7.27 (m, 1H), 7.19 (app t, J = 8.8 Hz, 1H), 7.10 (m, 4H), 6.95 (app t, J = 8.8 Hz, 2H), 5.74 (d, J = 8 Hz, 1H), 5.40 (br s, 1H), 5.08 (s, 2H), 4.47 (d J = 6 Hz, 2H) ppm. ^{19}F NMR (400 MHz, CDCl_3) δ -112.67 (1 F), -
- 10 116.39 (1 F) ppm. ES-HRMS m/z 439.0047 ($M+H$ calcd for $\text{C}_{19}\text{H}_{15}\text{ClBrF}_2\text{N}_2\text{O}$ requires 439.0019).

Example 499



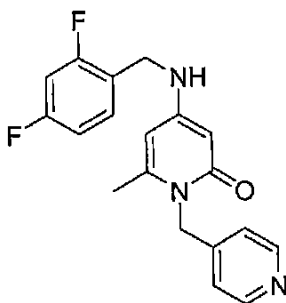
- 15 The title compound was prepared essentially as in Example 495. ^1H NMR (400 MHz, CDCl_3) δ 7.35- 7.2 (m, 1H), 7.27 (dd, J = 2.5 and 8 Hz, 1H), 7.05 (app d, J = 7.2 Hz, 3H), 6.97 (m, 4H), 5.72 (d, J = 7.6 Hz, 1H), 5.41 (br s, 1H), 5.08 (s, 2H), 4.46 (d, J = 6.4 Hz, 2H) ppm. ^{19}F NMR (400 MHz, CDCl_3) δ -112.5 (1
- 20 F), -113 (1 F) ppm. ES-HRMS m/z 405.0431 ($M+H$ calcd for $\text{C}_{19}\text{H}_{16}\text{BrF}_2\text{N}_2\text{O}$ requires 405.0409).

Example 500



Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-
 5 1-(pyridin-4-ylmethyl)pyridin-2(1H)-one .

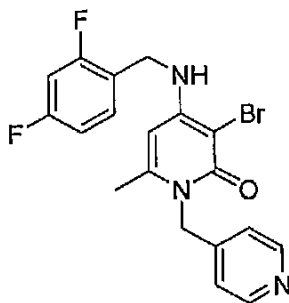
Step 1 Preparation of 4-[(2,4-difluorobenzyl)amino]-6-methyl-
 1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



10 (0.3 g, 1.39 mmol) and 2,4-difluoro benzylamine (1 mL,
 8.4 mmol) were combined in a nitrogen flushed culture tube.
 The tube was capped and heated at 180 C for 24 h. The excess
 amine was distilled in vacuo. ¹H NMR (400 MHz, CD₃OD) δ 8.44
 (dd, J = 1.7 and 4.8Hz, 2H), 7.38 (q, J = 10 and 15 Hz, 1H),
 15 7.14 (d, J = 4.8 Hz, 2H), 6.95 (m, 2H), 5.90 (dd, J = 1 and
 2.5Hz, 1H), 5.47 (d, J = 2, 1H), 5.28 (s, 2H), 4.33 (s, 2H),
 2.27 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -113.73 (1 F), -
 116.66 (1 F) ppm. ES-HRMS m/z 342.1422 (M+H calcd for
 C₁₉H₁₈F₂N₃O requires 342.1418).

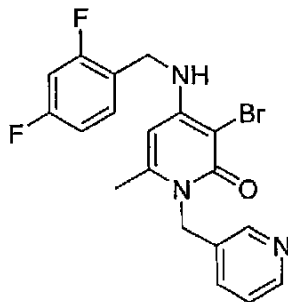
20

Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-
 methyl-1-(pyridin-4-ylmethyl)pyridin-2(1H)-one



N-Bromo succinimide (77 mg, 0.43 mmol) was added to a solution of the product of Step 1 (0.14 g, 0.41 mmol) in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction was complete by LC-MS. The reaction mixture was poured into saturated aqueous NaHCO₃. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was triturated with hexanes to give the title compound as a yellow solid (81 mg, 47 %). ¹H NMR (400 MHz, CDCl₃) δ 8.47 (dd, J = 1.6 and 4.8 Hz, 2H), 7.24 (q, J = 6.4 and 13.6 Hz, 1H), 7.01 (d, J = 6.4 Hz, 2H), 6.83 (m, 2H), 5.68 (s, 1H), 5.25 (s, 2H), 4.45 (d, J = 6.4 Hz, 2H), 2.12 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CDCl₃) δ -110.51 (m, 1 F), -114.66 (m, 1 F) ppm. ES-HRMS m/z 420.0524 (M+H calcd for C₁₉H₁₇BrF₂N₃O requires 420.0523).

Example 501

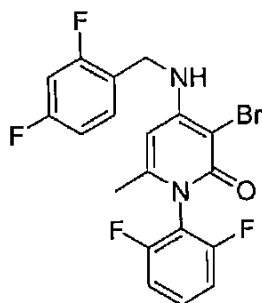


Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-6-methyl-1-(pyridin-3-ylmethyl)pyridin-2(1H)-one

The title compound was prepared essentially as in Example 500.

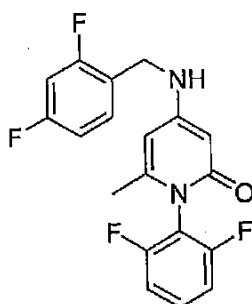
^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, $J = 4.8\text{Hz}$, 2H), 7.55 (app t, $J = 6\text{ Hz}$, 1H), 7.21 (m, 2H), 6.83 (m, 2H), 5.65 (s, 1H), 5.34 (d, $J = 5.2\text{Hz}$, 1H), 5.27 (s, 2H), 4.45 (s, 2H), 2.10 (d, $J = 4.8\text{Hz}$, 3H) ppm. ^{19}F NMR (400 MHz, CDCl_3) δ -110.74 (1 F), -114.86 (1 F) ppm. ES-HRMS m/z 420.0533 ($M+H$ calcd for $\text{C}_{19}\text{H}_{17}\text{BrF}_2\text{N}_3\text{O}$ requires 420.0523).

Example 502



Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

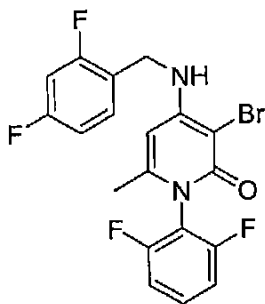
Step 1 Preparation of 4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one



1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.3 g, 1.26 mmol) and 2,4-difluorobenzylamine (1mL, 8.4 mmol) were combined in a nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was

chromatographed on silica (1:1 hexanes: ethyl acetate). The compound was approximately 50% pure and was carried on without further purification (0.633 g). ^1H NMR (400 MHz, CD_3OD) δ 7.53 (m, 1H), 7.41 (m, 1H), 7.16 (t, $J = 8.8\text{Hz}$, 2H), 6.93 (m, 2H), 6.00 (s, 1H), 5.42 (s, 1H), 5.42 (s, 1H), 4.37 (s, 2H), 1.93 (s, 3H) ppm. LC/MS, $t_r = 4.65$ minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 363 ($\text{M}+\text{H}$).

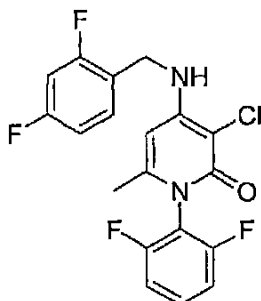
- 10 Step 2 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one



- N-Bromo succinimide (168 mg; 0.945 mmol) was added to a solution of the product of Step 1 (0.633 g) in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction was 50 % complete by LC-MS. Additional N-bromo succinimide (150 mg) was added and the reaction was stirred at 25 C for 12 h. The reaction mixture was poured into saturated aqueous NaHCO_3 . The aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was purified by reverse phase chromatography (60:40 Acetonitrile: water with 0.05% trifluoroacetic acid). The title compound was isolated as the TFA salt (0.161g, 23%). ^1H NMR (400 MHz, CD_3OD) δ 7.53 (m, 1H), 7.35 (q, $J = 8, 15.6\text{Hz}$, 1H), 7.16 (t, $J = 8\text{ Hz}$, 2H), 6.96 (app q, $J = 8, 16.4\text{Hz}$, 2H), 6.12 (s, 1H), 4.86 (s, 2H), 1.94 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -

77.33 (1 F), -113.60 (1 F), -116.63 (1F), -121.50 (1F) ppm.
ES-HRMS m/z 441.0231 (M+H calcd for C₁₉H₁₄BrF₄N₂O requires 441.0220).

5 Example 503

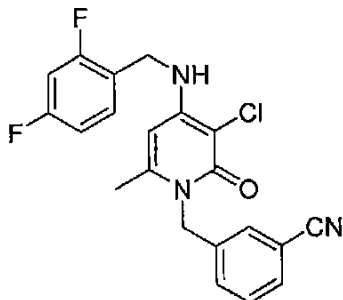


Preparation of 3-chloro-4-[(2,4-difluorobenzyl)amino]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

10 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (0.3 g, 1.26 mmol) and 2,4-difluoro benzylamine (1mL, 84 mmol) were combined in an nitrogen flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was used without
15 further purification. N-Chloro succinimide (168 mg, 1.26 mmol) was added to a solution of the residue in methylene chloride (10 mL). After stirring at 25 C for 1 h, the reaction mixture was poured into saturated aqueous NaHCO₃. The aqueous mixture was extracted with ethyl acetate. The organic
20 layer was washed with brine, dried with anhydrous Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica (25:75 hexanes: ethyl acetate) to give the title compound (32 mg, 6%). ¹H NMR (400 MHz, CD₃OD) δ 7.55 (m, 1H), 7.36 (q, J = 9.2 and 15.2Hz, 1H), 7.18 (t, J = 7.6Hz, 2H),
25 6.98 (m, 2H), 6.15 (s, 1H), 4.62 (s, 2H), 1.96 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -113.78 (1 F), -116.72 (1 F), -121.57

(1F) ppm. ES-HRMS m/z 397.0752 (M+H calcd for $C_{19}H_{14}ClF_4N_2O$ requires 397.0725).

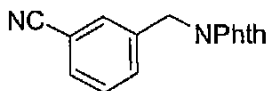
Example 504



5

Preparation of 3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

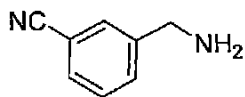
Step 1 Preparation of 3-phthalimidomethyl-benzonitrile



10

3-Phthalimidomethyl-benzonitrile was prepared as described in the literature. (Bookser, B.C.; Bruice, T.C. J. Am. Chem. Soc. 1991, 113, 4208-18.)

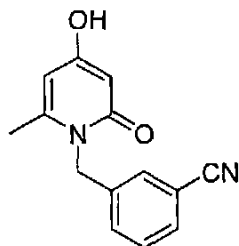
15 Step 2 Preparation of 3-(aminomethyl)benzonitrile



3-(Aminomethyl)benzonitrile was prepared as described in the literature. (Bookser, B.C.; Bruice, T.C. J. Am. Chem. Soc. 1991, 113, 4208-18.)

20

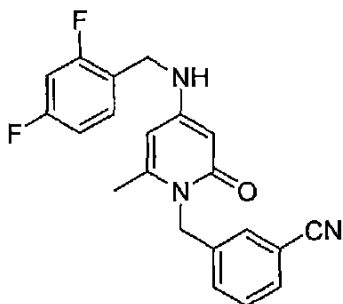
Step 3 Preparation of 3-[(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)methyl]benzonitrile



A nitrogen flushed pyrex reaction tube was charged with 3-(aminomethyl)benzonitrile (1 g, 7.9 mmol), 4-hydroxy-6-methyl-2-pyridone (1 g, 7.9 mmol) and water (20 mL). The tube
 5 was capped and was heated to reflux. After 1.5 h, the product precipitated from solution. The reaction mixture was cooled to room temperature, filtered and washed with water. The product was used without further purification (1.67g, 88 %).

¹H NMR (400 MHz, dms_o-d₆) δ 10.53 (s, 1H), 7.61 (d, J = 8Hz, 1H), 7.52 (t, J = 8Hz, 2H), 7.38 (d, J = 8 Hz, 1H), 5.79 (dd, J = 1 and 2.5 Hz, 1H), 5.56 (d, J = 2.7 Hz, 1H), 5.18 (s, 2H), 2.14 (s, 3H) ppm. ES-HRMS m/z 241.0968 (M+H calcd for C₁₄H₁₃N₂O₂ requires 241.0972).

15 Step 5 Preparation of 3-{[4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile

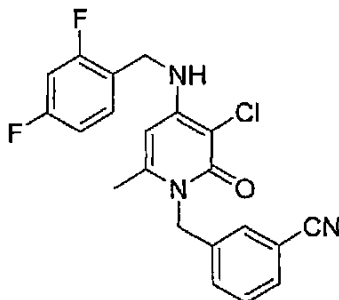


The product from Step 4 (0.5 g, 2.08 mmol) and 2,4-difluorobenzylamine (2mL, 16.8 mmol) were combined in a nitrogen
 20 flushed culture tube. The tube was capped and heated at 180 C for 24 h. The excess amine was distilled in vacuo and the residue was triturated with ethyl acetate/ hexanes to precipitate the starting materials. The residue was

chromatographed on reverse phase (1:1 water: acetonitrile with 0.05% trifluoroacetic acid). The product of Step 5 was isolated as a white semi-solid (0.125g, 15%). ¹H NMR (400 MHz, CD₃OD) δ 7.61(d, J = 8Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 7.41 (m, 3H), 6.94 (m, 2H), 5.89 (dd, J = 0.8 and 2.7Hz, 1H), 5.47 (d, J = 2.8Hz, 1H), 5.27 (s, 2H), 4.34 (s, 2H), 2.18 (s, 3H) ppm. LC/MS, t_r = 4.87 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 366 (M+H).

10

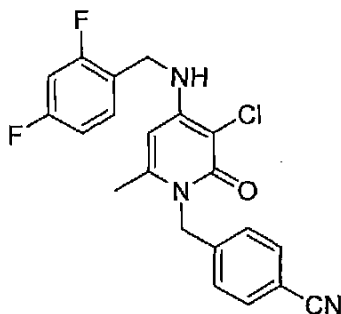
Step 6 Preparation of 3-{[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzonitrile



15 N-Chloro succinimide (36 mg, 0.27 mmol) was added to a solution of the product of Step 5 (0.125 g, 0.26 mmol) in methylene chloride (10 mL). After stirring at 25 C for 2 h, the reaction was complete by LC-MS. The reaction mixture was poured into saturated aqueous NaHCO₃. The aqueous mixture was
20 extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na₂SO₄, and concentrated in vacuo. The residue was triturated with acetonitrile to give the title compound as a tan solid (20 mg, 13%). ¹H NMR (400 MHz, CD₃OD) δ 7.61 (d, J = 8.4 Hz, 1H), 7.49 (m, 2H), 7.40 (d, J = 8.4 Hz, 1H), 7.33 (q, J = 8.4 and 14.8 Hz, 1H), 6.94 (m, 2H), 6.00 (s, 1H), 5.34 (s, 2H), 4.56 (s, 2H), 2.21 (s, 3H)
25 ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -114.00 (1 F), -116.89 (1 F)

ppm. LC/MS, t_r = 5.49 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 400 ($M+H$).

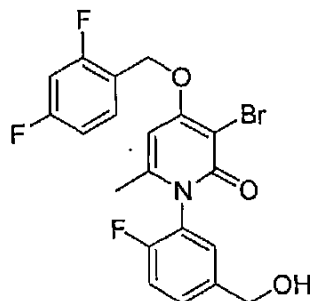
5 Example 505



Preparation of 4-[[3-chloro-4-[(2,4-difluorobenzyl)amino]-6-methyl-2-oxopyridin-1(2H)-yl]methyl]benzonitrile

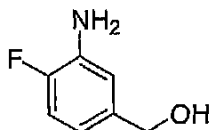
10 The title compound was prepared essentially as in Example 504. ^1H NMR (400 MHz, CD_3OD) δ 7.66 (d, J = 8 Hz, 2H), 7.33 (q, J = 8 and 15.2 Hz, 1H), 7.25 (d, J = 8 Hz, 2H), 6.94 (m, 2H), 6.01 (s, 1H), 5.36 (s, 2H), 4.55 (s, 2H), 2.19 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -77.52 (1F), -113.89 (1 F), -116.71 (1 F) ppm. LC/MS, t_r = 5.49 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 400 ($M+H$).

Example 506



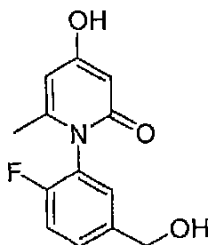
20 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

Step 1 Preparation of (3-amino-4-fluorophenyl)methanol



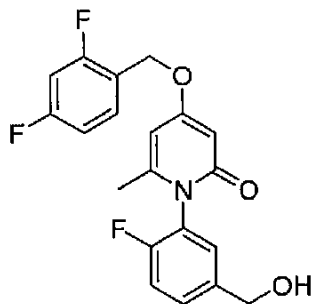
5 A flask equipped with overhead stirrer was charged with 4-fluoro-3-nitrobenzyl alcohol (20g, 0.117 mol) and 200 mL of 5:1 isopropanol: water. Ammonium chloride (62 g, 1.17 mol) was added followed by iron filings (65g, 1.17 mol). The mixture was stirred at 70 C for 1.5 H when it was shown to be
10 complete by LC-MS. The liquid was decanted and the solids were washed with additional isopropanol: water. The isopropanol was removed and the residue was diluted with 0.5 N HCl and was extracted with ethyl acetate. The aqueous layer was brought to pH 12-14 with 2.5 N NaOH and was extracted with
15 ethyl acetate. The organic layer was dried with anhydrous Na₂SO₄ and concentrated in vacuo. 3-Amino-4-fluorophenyl methanol was isolated as a brown solid (4.5g, 27%) and was used without further purification. LC/MS, *t_r* = 2.40 minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with
20 detection 254 nm, at 50°C). ES-MS *m/z* 142 (M+H). ES-HRMS *m/z* 142.0692 (M+H calcd for C₇H₈FNO requires 142.0663).

Step 2 Preparation of 1-[2-fluoro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one



A 100 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with (3-amino-4-fluorophenyl)methanol (4.5 g, 31.9 mmol), 4-hydroxy-6-methyl-2-pyrone (4 g, 31.9 mmol) and o-dichlorobenzene (5 mL). The system was immersed in a 170 C oil bath for 10 minutes. The solvent was removed in vacuo and the residue was chromatographed on reverse phase (75:25 water:acetonitrile with 0.05% TFA). The product contained some starting materials after purification and was used without further purification (1.27g, 15%). ¹H NMR (400 MHz, dms_o-d₆) δ 7.39 (m, 1H), 7.20 (dd, J = 2.2 and 7.6 Hz, 1H), 6.74 (dd, J = 2.7 and 9.6 Hz, 1H), 5.93 (dd, J = 1.2 and 2.2 Hz, 1H), 5.22 (dd, J = 0.4 and 2.2 Hz, 1H), 2.12 (s, 3H) ppm. ES-HRMS m/z 250.0862 (M+H calcd for C₁₃H₁₃FNO₃ requires 250.0874).

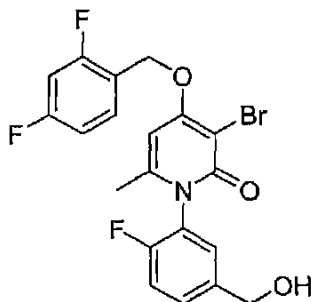
Step 3 Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one



A 100 mL roundbottomed flask (nitrogen purged) was charged with 1-[2-fluoro-5-(hydroxymethyl)phenyl]-4-hydroxy-6-methylpyridin-2(1H)-one (1.2g, 4.82 mmol) and N,N-dimethylformamide (10 mL). Potassium carbonate (0.6g, 4.4 mmol) and 2,4-difluorobenzyl bromide (0.56 mL, 4.4 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with saturated aqueous NaHCO₃ and extracted with ethyl acetate. The organic

layer was concentrated in vacuo and the residue was chromatographed on silica (9:1 methylene chloride: ethanol). The impure oil (0.3g, 17%) was carried on without further purification. ^1H NMR (400 MHz, CD_3OD) δ 7.54 (m, 2H), 7.30 (m, 2H), 7.02 (m, 2H), 6.17 (dd, $J = 1$ and 2.8 Hz, 1H), 6.03 (d, $J = 2.8$ Hz, 1H), 5.14 (s, 2H), 4.62 (s, 2H), 2.14 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.35 (1F), -115.97 (1 F), -127.31 (1 F) ppm. LC/MS, $t_r = 5.05$ minutes (5 to 95% acetonitrile/water over 8 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 375 ($\text{M}+\text{H}$).

Step 4 Preparation of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[2-fluoro-5-(hydroxymethyl)phenyl]-6-methylpyridin-2(1H)-one

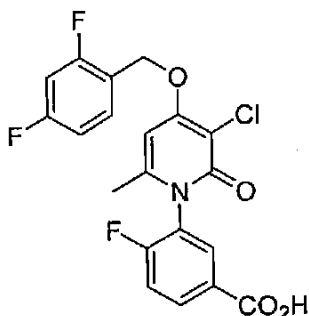


N-Bromo succinimide (50 mg, 0.3 mmol) was added to a solution of the product of Step 3 (0.12 g, 0.32 mmol) in N,N-dimethyl formamide (4 mL). After stirring at 25 C for 2 h, trifluoroacetic acid (50 μL) was added. After 1 h, additional N-Bromo succinimide (30 mg) was added. After 1 h, the reaction was complete by LC-MS. The reaction mixture was poured into brine and was extracted with ethyl acetate. The organic layer was washed with brine, dried with anhydrous Na_2SO_4 , and concentrated in vacuo. The residue was chromatographed on reverse phase (95:5 methylene chloride: ethanol). The title compound was isolated as the TFA salt (38 mg, 26 %). ^1H NMR (400 MHz, CD_3OD) δ 7.64 (q, $J = 7.6$ and 14.8 Hz, 1H), 7.51 (m, 1H), 7.31 (app t, $J = 8.4$ Hz, 1H), 7.04 (t,

$J = 8.4$ Hz, 2H), 6.63 (s, 1H), 5.34 (s, 2H), 4.62 (s, 2H), 2.06 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.48 (1F), -115.92 (1 F), -127.23 (1 F) ppm. ES-HRMS m/z 454.0228 (M+H calcd for $\text{C}_{20}\text{H}_{16}\text{BrF}_3\text{NO}_3$ requires 454.0260).

5

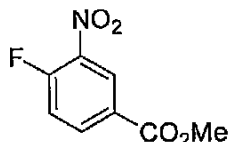
Example 507



Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid

10

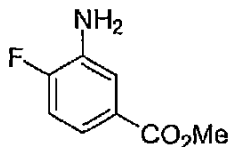
Step 1 Preparation of methyl 4-fluoro-3-nitrobenzoate



A 1 L 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 4-fluoro-3-nitrobenzoic acid (50 g, 0.27 mol) and methanol (300 mL). The system was cooled to 0 C and acetyl chloride (27 mL, 0.37 mol) was added dropwise. The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 1.5 h. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NaHCO_3 , and extracted with ethyl acetate. The organic extract was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to give methyl 4-fluoro-3-nitrobenzoate as an orange solid (40.6 g, 75%). ^1H NMR (400 MHz, CD_3OD) δ 8.67 ((dd, $J = 2.2$ and 6.8 Hz, 1H), 8.34 (dddd, J

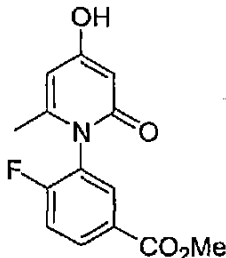
= 2.2, 4.4, 6.4 and 8.8 Hz, 1H), 7.55 (dd, J = 8.8 and 10.8 Hz, 1H), 3.94 (s, 3H) ppm. ES-HRMS m/z 200.02446 (M+H calcd for C₈H₇FNO₄ requires 200.0354).

5 Step 2 Preparation of methyl 3-amino-4-fluorobenzoate



A Parr bottle was charged with the product of Step 1 (40 g, 0.2 mol), ethanol (400 mL) and 10% Pd/C (1 g/g). The system was flushed twice with nitrogen and hydrogen. The reaction mixture was hydrogenated at 40 psi until no starting material was visible by LC-MS. The reaction mixture was slurried with Celite and then was filtered through a pad of celite. The filtrate and ensuing ethanol washes were concentrated in vacuo to give methyl 3-amino-4-fluorobenzoate as an orange solid (30.6 g, 91%). ¹H NMR (400 MHz, CD₃OD) δ 7.54 (d, J = 8.7 Hz, 1H), 7.35 (m, 1H), 7.06 (t, J = 8.7 Hz, 1H), 3.09 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -131.02 (1F) ppm. ES-HRMS m/z 199.0281 (M+H calcd for C₈H₇FNO₄ requires 199.02).

20 Step 3 Preparation of methyl 4-fluoro-3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate

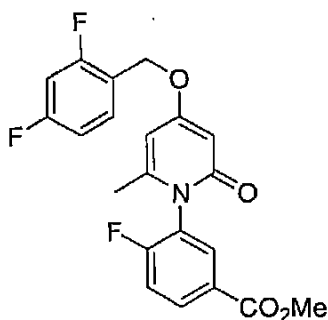


A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 3 (30 g, 0.18 mol), 4-hydroxy-6-methyl-2-pyrone (22.6 g, 0.18 mol), and o-dichlorobenzene (90 mL). The

system was immersed in a 170 C oil bath for 30 minutes and was then cooled to room temperature. The reaction mixture was washed with aqueous Na₂CO₃ (38 g, 0.36 mol, 300 mL water). The aqueous layer was washed with ethyl acetate and then was
5 acidified to pH 1-2 with concentrated HCl. This was extracted with ethyl acetate, which was then dried with MgSO₄ and concentrated in vacuo. The viscous orange oil was used without further purification (14.4 g, 28%). ¹H NMR (400 MHz, CD₃OD) δ 8.18 (dddd, J = 2.3, 5.2, 7.2 and 8.8 Hz, 1H), 7.97
10 (dd, J = 2 and 7.2 Hz, 1H), 7.44 (t, J = 8.8 Hz, 1H), 6.09 (d, J = 1.8 Hz, 1H), 5.78 (d, J = 2.4 Hz, 1H), 3.9 (s, 3H), 2.14 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -117.29 (1F) ppm. ES-HRMS m/z 278.0796 (M+H calcd for C₁₄H₁₃FNO₄ requires 278.0823).

15

Step 4 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate

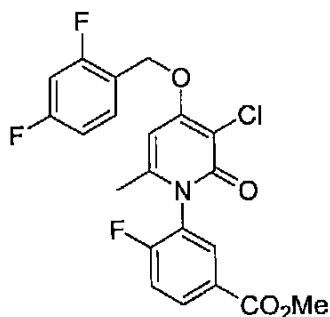


A 100 mL round bottomed flask equipped with stirbar and
20 nitrogen inlet was charged with the product of Step 3 (14.4 g, 51.9 mmol) and N,N-dimethyl formamide (40 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (10.9 mL, 72.8 mmol) was added followed by 2,4-difluorobenzyl bromide (9.3 mL, 72.8 mmol). The reaction mixture was stirred at 65 C for 18 h, was poured
25 into saturated aqueous NaHCO₃ and was extracted with ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated in vacuo to give the title product, as

an orange oil (21.5g), which was carried on to the next reaction without further purification. ^1H NMR (400 MHz, CD_3OD) δ 8.20 (dddd, $J = 2.2, 4.8, 7.2$ and 8.8 Hz, 1H), 8.00 (dd, $J = 2.2$ and 7.2 Hz, 1H), 7.56 (td, $J = 2.4, 6.4$ and 9.2 Hz, 1H), 7.46 (t, $J = 9.2$ Hz, 1H), 7.02 (m, 2H), 6.18 (dd, $J = 0.8$ and 2.6 Hz, 1H), 6.04 (d, $J = 2.7$ Hz, 1H), 5.14 (s, 2H), 3.90 (s, 3H), 1.98 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.34 (1F), -116.00 (1 F), -117.35 (1 F) ppm. ES-HRMS m/z 404.1104 (M+H calcd for $\text{C}_{21}\text{H}_{17}\text{F}_3\text{NO}_4$ requires 404.1104).

10

Step 5 Preparation of methyl 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate

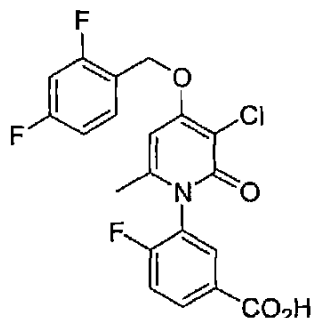


15 A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 4 (21 g, 52 mmol) and N-methyl-2-pyrrolidine (100 mL). N-Chloro succinimide (8.3 g, 62 mmol) was added and the reaction mixture was stirred at 65 C for 2 h. The mixture was then
20 cooled to room temperature, poured into saturated aqueous NaHCO_3 and extracted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 , and concentrated in vacuo. The residue was triturated with diethyl ether and filtered to give the title compound, as a white powder (5.9 g,
25 25%). ^1H NMR (400 MHz, CD_3OD) δ 8.22 (dddd, $J = 2, 4.8, 6.8$ and 8.8 Hz, 1H), 8.03 (dd, $J = 2$ and 7.2 Hz, 1H), 7.62 (q, $J = 8.4$ and 14.8 Hz, 1H), 7.48 (t, $J = 14$ Hz, 1H), 7.04 (m, 2H),

6.69 (s, 1H), 5.36 (s, 2H), 3.91 (s, 3H), 2.08 (s, 3H) ppm.
¹⁹F NMR (400 MHz, CD₃OD) δ -111.38 (1F), -115.97 (1 F), -117.43 (1 F) ppm. ES-HRMS m/z 438.0723 (M+H calcd for C₂₁H₁₆ClF₃NO₄ requires 438.0714).

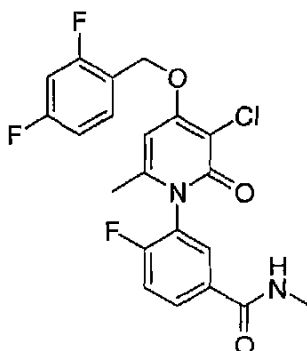
5

Step 6 Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid



A 100 mL round bottomed flask was charged with the
10 product of Step 5 (2.5 g, 5.72 mmol), tetrahydrofuran (40 mL),
methanol (10 mL), and water (10 mL). To this slurry was added
2.5 N NaOH (4.6 mL, 11.4 mmol). The reaction mixture became
clear after 5 minutes and the reaction was complete in 35
minutes by LC-MS. The organics were removed on the rotary
15 evaporator and the remaining solution was acidified to pH 3
with 6N HCl. The desired compound was precipitated by the
addition of diethyl ether and subsequent filtration. The
title compound was isolated as a white powder (2.5 g, 98%). ¹H
NMR (400 MHz, dms^o-d₆) δ 8.10 (dddd, J = 2.1, 4.8, 7.2 and 8.4
20 Hz, 1H), 8.00 (dd, J = 2.1 and 7.6 Hz, 1H), 7.66 (q, J = 9.2
and 15.6 Hz, 1H), 7.57 (t, J = 8.8 Hz, 1H), 7.34 (td, J = 2.4
and 10.4 Hz, 1H), 7.17 (tdd, J = 1, 2.7 and 8.4 Hz, 1H), 6.76
(s, 1H), 5.33 (s, 2H), 1.98 (s, 3H) ppm. ¹⁹F NMR (400 MHz,
dms^o-d₆) δ -109.32 (1F), -113.64 (1 F), -117.22 (1 F) ppm.
25 ES-HRMS m/z 424.0575 (M+H calcd for C₂₀H₁₄ClF₃NO₄ requires
424.0558).

Example 508



Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-methylbenzamide

5

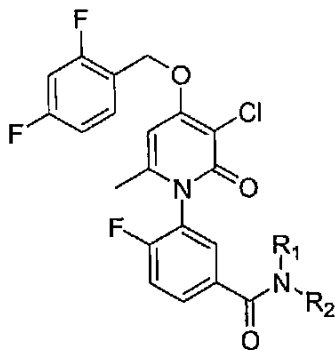
To a reaction vessel (borosilicate culture tube) was added 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (0.300 g, 0.708 mmol) and 1-hydroxybenzotriazole (0.048 g, 0.45 mmol). N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately 1.2 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional N,N-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. N-Methyl amine (1 mL, 2 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2.17 g of polyamine resin (2.63 mmol/g) and approximately 2.8 g of methylisocyanate functionalized polystyrene (1.5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble

25

byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N₂ over the vial and the resulting solid was triturated with diethyl ether to give an off-white solid. (0.168 g, 59%)

- 5 ¹H NMR (400 MHz, CD₃OD) δ 8.02 (dddd, J = 2, 4.4, 7.2 and 8.4 Hz, 1H), 7.80 (dd, J = 2 and 6.8 Hz, 1H), 7.62 (q, J = 8 and 14.4 Hz, 1H), 7.34 (t, J = 8.8 Hz, 1H), 7.04 (m, 2H), 6.69 (s, 1H), 5.36 (s, 2H), 3.29 (s, 3H), 1.98 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -108.94 (1F), -113.55 (1 F), -117.76 (1 F) ppm. ES-HRMS m/z 437.0861 (M+H calcd for C₂₁H₁₇ClF₃N₂O₃ requires 437.0874).

Examples 509-518 ,

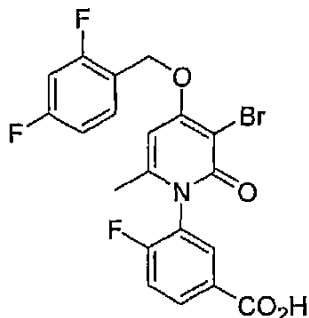


- 15 By following the method of Example 508 and replacing N-methylamine with the appropriate amine, the compounds of Examples 509-518 are prepared.

Example No.	R ₁	R ₂	% Yield	MF	M+H Requires	ESHRMS m/z
Ex. 509	CH ₃	CH ₃	59	C ₂₂ H ₁₉ ClF ₃ N ₂ O ₃	451.1031	451.1016
Ex. 510	H	CH ₂ CH ₂ OH	70	C ₂₂ H ₁₉ ClF ₃ N ₂ O ₄	467.0980	467.0985
Ex. 511	CH ₂ CH ₂ N(C H ₃) -	CH ₂ CH ₂ N(C H ₃) -	70	C ₂₅ H ₂₄ ClF ₃ N ₃ O ₃	506.1453	506.1447
Ex. 512	CH ₂ CH ₂ O-	CH ₂ CH ₂ O-	19	C ₂₄ H ₂₁ ClF ₃ N ₂ O ₄	493.1101	493.1136
Ex. 513	H	CH ₂ CH ₂ OCH ₃	59	C ₂₃ H ₂₁ ClF ₃ N ₂ O ₄	481.1136	481.1136

Ex. 514	CH ₃	CH ₂ CH ₂ OH	63	C ₂₃ H ₂₁ ClF ₃ N ₂ O ₄	481.1136	481.1131
Ex. 515	H	CH ₂ CH ₂ CH ₂ O H	51	C ₂₃ H ₂₁ ClF ₃ N ₂ O ₄	481.1136	481.1121
Ex. 516	H	CH ₂ CH(OH) CH ₂ OH	64	C ₂₃ H ₂₁ ClF ₃ N ₂ O ₅	497.1086	497.1102
Ex. 517	H	C(CH ₃) ₂ CH ₂ OH-	54	C ₂₄ H ₂₃ ClF ₃ N ₂ O ₄	495.1293	495.1303
Ex. 518	CH ₂ CH ₂ NH-	CH ₂ CH ₂ NH-	34	C ₂₃ H ₂₂ ClF ₃ N ₃ O ₃	491.89	

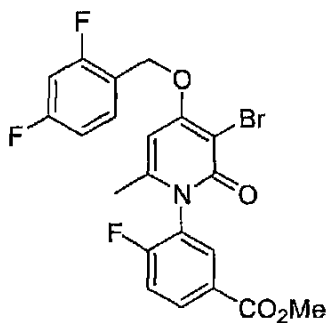
Example 519



- 5 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid

Step1 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoate

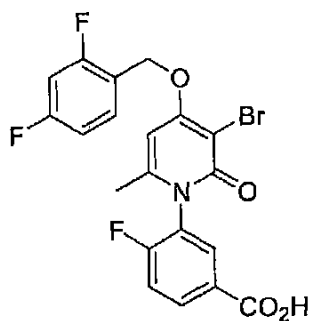
10 fluorobenzoate



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-

fluorobenzoate (7.3 g, 18 mmol) and N-methyl-2-pyrrolidine (20 mL). N-Bromo succinimide (3.5 g, 19.8 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes. The mixture poured into saturated aqueous NaHCO₃ and
5 extracted with ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, and concentrated in vacuo. The residue was triturated with diethyl ether and filtered to give the title compound as a white powder (3.49 g). ¹H NMR (400 MHz, CD₃OD) δ 8.16 (qd, J = 3, 6.8 and 15.6 Hz, 1H), 7.84 (d, J = 2.12 Hz, 1H), 7.64 (q, J = 8.4 and 14.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.04 (m, 2H), 6.60 (s, 1H), 5.34 (s, 2H), 3.87 (s, 3H), 2.00 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -111.51 (1F), -115.98 (1F), -117.43 (1F) ppm. ES-HRMS m/z 494.0387 (M+H calcd for C₂₂H₁₉BrF₂NO₅ requires 494.0409).

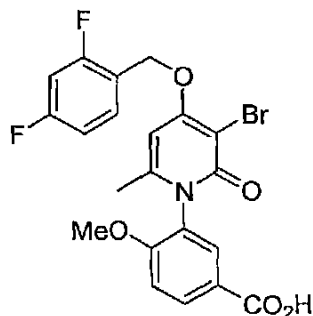
Step 2 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid



A 100 mL round bottomed flask was charged with the
20 product of Step 2 (3.4 g, 7.05 mmol), tetrahydrofuran (40 mL), methanol (10 mL), and water (10 mL). To this slurry was added 2.5 N NaOH (5.6 mL, 14.1 mmol). The reaction mixture became clear after 5 minutes and the reaction was complete in 1 h by LC-MS. The organics were removed on the rotary evaporator and
25 the remaining solution was acidified to pH 1-2 with 6N HCl. The desired compound was precipitated by the addition of water and diethyl ether and subsequent filtration. The title

compound was isolated as a white powder (2.64 g, 80%). ^1H NMR (400 MHz, CD_3OD) δ 8.21 (dddd, $J = 2.4, 5.2, 7.2$ and 9.2 Hz, 1H), 8.00 (dd, $J = 2.0$ and 7.2 Hz, 1H), 7.65 (q, $J = 8.4$ and 14.8 Hz, 1H), 7.45 (t, $J = 8.4$ Hz, 1H), 7.04 (appt, $J = 9.6$ Hz, 1H), 6.65 (s, 1H), 5.36 (s, 2H), 2.07 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.40 (1F), -116.00 (1 F), -118.36 (1 F) ppm. ES-HRMS m/z 480.0259 ($M+H$ calcd for $\text{C}_{21}\text{H}_{17}\text{BrF}_2\text{NO}_5$ requires 480.0253).

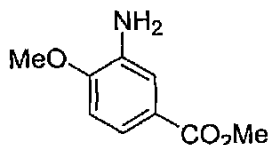
10 Example 520



Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoic acid

15

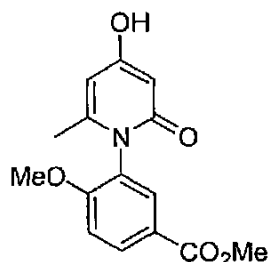
Step 1 Preparation of methyl 3-amino-4-methoxybenzoate



A 1 L 3-necked round bottomed flask equipped with a nitrogen inlet, stirbar, addition funnel and thermocouple was charged with 3-amino-4-methoxy benzoic acid (50 g, 0.299 mol) and methanol (300 mL). The system was cooled to 0°C and acetyl chloride (30 mL, 0.42 mol) was added dropwise. The system was warmed to room temperature, the addition funnel was replaced with a reflux condensor, and was heated to reflux for 1.5 h. The reaction mixture was cooled to room temperature,

quenched with saturated aqueous NaHCO_3 , and extracted with ethyl acetate. The organic extract was washed with brine, dried with Na_2SO_4 and concentrated in vacuo to give methyl 3-amino-4-methoxybenzoate as a dark solid (47.9 g, 88%). ^1H NMR (400 MHz, CD_3OD) δ 7.40 (t, $J = 2.68$ Hz, 1H), 7.37 (t, $J = 2.0$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 1H), 3.98 (s, 3H), 3.81 (s, 3H) ppm. ES-HRMS m/z 182.0826 ($M+H$ calcd for $\text{C}_9\text{H}_{12}\text{ClNO}_3$ requires 182.0812).

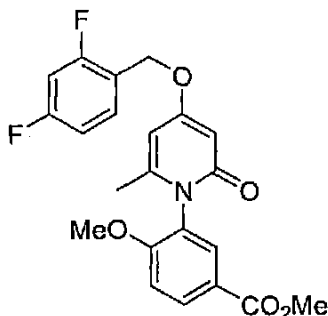
10 Step 2 Preparation of methyl 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-methoxybenzoate



A 250 mL round bottomed flask equipped with stirbar, Dean-Stark trap and reflux condensor was charged with the product of Step 1 (23.5 g, 0.129 mol), 4-hydroxy-6-methyl-2-pyrone (17.8 g, 0.14 mol), and o-dichlorobenzene (200 mL). The system was immersed in a 170 C oil bath for 2 h and was then cooled to room temperature. The reaction mixture was washed with aqueous Na_2CO_3 (28 g, 0.26 mol, 500 mL water). The aqueous layer was washed with ethyl acetate and then was acidified to pH 1-2 with concentrated HCl. This was extracted with ethyl acetate, which was then dried with Na_2SO_4 and concentrated in vacuo. The viscous orange oil was triturated with MeOH to give the title compound as a yellow solid (1.61 g, 4%). ^1H NMR (400 MHz, CD_3OD) δ 8.14 (dd, $J = 2.2$ and 8.8 Hz, 1H), 7.79 (d, $J = 2.2$ Hz, 1H), 7.27 (d, $J = 8.8$ Hz, 1H), 6.05 (d, $J = 2.3$ Hz, 1H), 5.77 (d, $J = 2.3$ Hz, 1H), 3.88 (s,

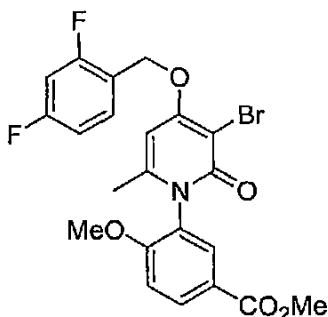
3H), 3.87 (s, 3H), 1.90 (s, 3H) ppm. ES-HRMS m/z 290.0997 (M+H calcd for C₁₅H₁₆NO₅ requires 290.1023).

Step 3 Preparation of methyl 3-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoate



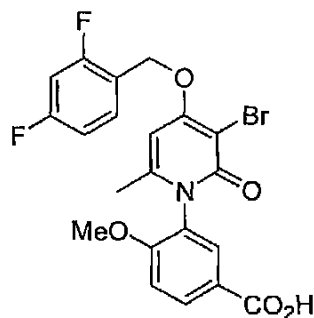
A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 2 (1.6 g, 5.5 mmol) and N,N-dimethyl formamide (10 mL). 1,8-diazabicyclo[5.4.0]undec-7-ene (0.91 mL, 6 mmol) was added followed by 2,4-difluorobenzyl bromide (0.77 mL, 6 mmol). The reaction mixture was stirred at 60 C for 4 h, was poured into saturated aqueous NaHCO₃ and was extracted with ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄ and concentrated in vacuo to give the title compound as an orange foam (2.13g, 93%), which was carried on to the next reaction without further purification. ¹H NMR (400 MHz, CD₃OD) δ 8.17 (dd, J = 2.64 and 11.6 Hz, 1H), 7.82 (td, J = 2.7 and 6.8 Hz, 1H), 7.57 (m, 1H), 7.29 (d, J = 11.6 Hz, 1H), 7.02 (m, 2H), 6.16 (m, 1H), 6.03 (d, J = 3.5 Hz, 1H), 5.14 (s, 2H), 3.89 (s, 6H), 1.93 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -111.43(1F), -116.04 (1 F) ppm. ES-HRMS m/z 416.1310 (M+H calcd for C₂₂H₂₀F₂NO₅ requires 416.1304).

Step 4 Preparation of methyl 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoate



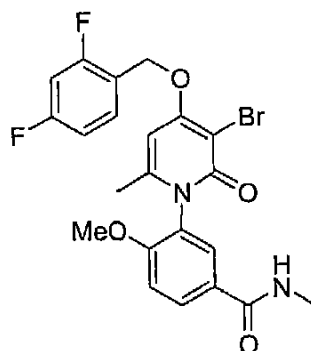
A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product of Step 3 (2.1 g, 5.06 mmol) and N-methyl-2-pyrrolidine (10 mL). N-Bromo succinimide (1 g, 5.56 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The mixture poured into saturated aqueous NaHCO₃ and extracted with ethyl acetate. The organic layer was washed with brine, dried with Na₂SO₄, and concentrated in vacuo. The residue was chromatographed on silica (1:1 hexanes: ethyl acetate) to give the title compound as an orange oil (0.77 g, 31%). ¹H NMR (400 MHz, CD₃OD) δ 8.16 (app qd, J = 2.5 and 7.2 Hz, 1H), 7.84 (d, J = 2.6 Hz, 1H), 7.64 (m, 1H), 7.30 (d, J = 9.2 Hz, 1H), 7.04 (appt, J = 8.4 Hz, 2H), 6.60 (s, 1H), 5.33 (s, 2H), 3.80 (s, 6H), 1.99 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -111.56 (1F), -116.00 (1 F) ppm. ES-HRMS m/z 494.0398 (M+H calcd for C₂₂H₁₉BrF₂NO₅ requires 494.0409).

Step 5 Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxybenzoic acid



A 100 mL round bottomed flask was charged with the product of Step 4 (0.77 g, 1.55 mmol), tetrahydrofuran (10 mL), methanol (5 mL), and water (5 mL). To this slurry was added 2.5 N NaOH (1.2 mL, 3.1 mmol). The reaction mixture
5 became clear after 30 minutes and the reaction was complete in 1 h by LC-MS. The organics were removed on the rotary evaporator and the remaining solution was acidified to pH 2-3 with 6N HCl. The desired compound was precipitated by the addition of water and diethyl ether and subsequent filtration.
10 The title compound was isolated as a white powder (0.60 g, 81%). ¹H NMR (400 MHz, CD₃OD) δ 8.17 (dd, J = 2.2 and 8.8 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.64 (q, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.34 (t, J = 8.8 Hz, 2H), 6.60 (s, 1H), 5.34 (s, 2H), 3.87 (s, 3H), 2.01 (s, 3H) ppm. ES-HRMS m/z 480.0259
15 (M+H calcd for C₂₁H₁₇BrF₂NO₅ requires 480.0253).

Example 521



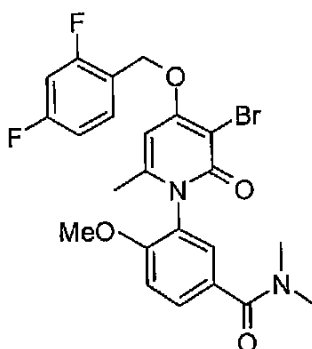
Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-
20 methyl-2-oxopyridin-1(2H)-yl]-4-methoxy-N-methylbenzamide

Step 1

To a reaction vessel (borosilicate culture tube) was added Example 520 (0.300 g, 0.624 mmol) and 1-hydroxybenzotriazole
25 (0.042 g, 0.31 mmol). N,N-Dimethylformamide (3 mL) was added to the reaction vessel followed by approximately 1.06 g of the polymer bound carbodiimide resin (1.38 mmol/g). Additional

N,N-dimethylformamide (2 mL) was then added to the reaction vessel. The parallel reaction apparatus was then orbitally shaken (Labline Benchtop Orbital Shaker) at approximately 200 RPM at room temperature for 15 minutes. N-Methyl amine (2 mL, 4 mmol) was then added to the reaction vessel and the reaction apparatus was orbitally shaken at room temperature overnight. At this time the reaction was diluted with tetrahydrofuran (20 mL) and treated with approximately 2 g of polyamine resin (2.63 mmol/g) and approximately 2.5 g of methylisocyanate functionalized polystyrene (1.5 mmol/g) and the orbital shaking was continued at 200 RPM at room temperature for 3 hours. The reaction vessel was then opened and the solution phase product was separated from the insoluble quenched byproducts by filtration and collection into a vial. After partially evaporation the insoluble byproducts were rinsed with tetrahydrofuran (2 x 10 mL). The filtrate was evaporated by blowing N₂ over the vial and the resulting solid was triturated with diethyl ether to give the desired product as an off-white solid (0.094 g, 31%). ¹H NMR (400 MHz, CD₃OD) δ 7.98 (dd, J = 2.2 and 8.8 Hz, 1H), 7.64 (m, 2H), 7.28 (d, J = 9.2 Hz, 1H), 7.04 (t, J = 9.2 Hz, 2H), 6.60 (s, 1H), 5.34 (s, 2H), 3.86 (s, 3H), 2.88 (s, 3H), 2.01 (s, 3H) ppm. ¹⁹F NMR (400 MHz, CD₃OD) δ -111.59 (1F), -116.01 (1F) ppm. ES-HRMS m/z 493.0593 (M+H calcd for C₂₂H₂₀BrF₂N₂O₄ requires 493.0569).

Example 522



Preparation of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methoxy-N,N-dimethylbenzamide

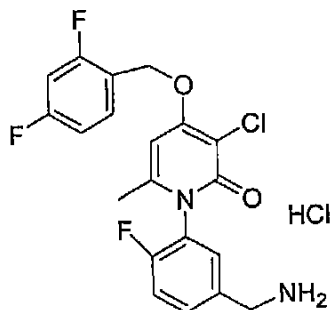
5

The title compound was prepared essentially as in Example 521.

^1H NMR (400 MHz, CD_3OD) δ 7.64 (m, 1H), 7.61 (dd, J = 2 and 8.8 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 7.04 (t, J = 8 Hz, 2H), 6.59 (s, 1H), 5.33 (s, 2H), 3.85 (s, 3H), 3.07 (s, 6H), 2.02 (s, 3H) ppm. ^{19}F NMR (400 MHz, CD_3OD) δ -111.60 (1F), -116.01 (1 F) ppm. ES-HRMS m/z 507.0716 ($M+H$ calcd for $\text{C}_{23}\text{H}_{22}\text{BrF}_2\text{N}_2\text{O}_4$ requires 507.0726).

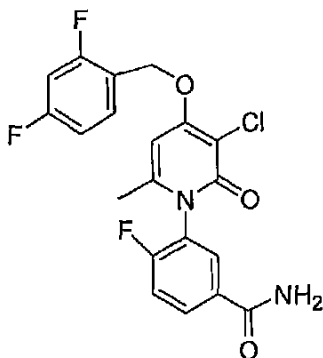
Example 523

15 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride



Step 1

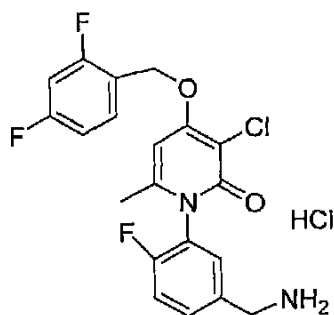
20 Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzamide



A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (2.58g, 6.1 mmol), 4-methylmorpholine (2.0 mL, 18.3 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.28g, 7.3 mmol) and tetrahydrofuran (30 mL). After stirring the mixture for 30 min at 25° C, NH₄OH (15.0 mL) was added. The mixture was stirred for 30 min and diluted with water. The product precipitated from solution. The precipitated was filtered and washed with water and diethyl ether to give the title compound (2.55g, 78%) as a white solid. ¹H NMR (400 MHz, (CD₃)₂SO) δ 8.10 (m, 1H), 7.9 (dd, J = 2.1 and 5.2 Hz, 1H), 7.65 (q, 6.7 and 8.5 Hz, 1H), 7.56 (t, J = 9.1 Hz, 1H), 7.35 (td, J = 2.4 and 8.2 Hz, 1H) 7.17 (td, J = 2 and 6.6 Hz, 1H) 6.78 (s, 1H), 5.36 (s, 2H), 2 (s, 3H) ppm. ES-HRMS m/z 423.0719 (M+H calcd for C₂₀H₁₅ClF₃N₂O₃ requires 423.0718).

Step 2

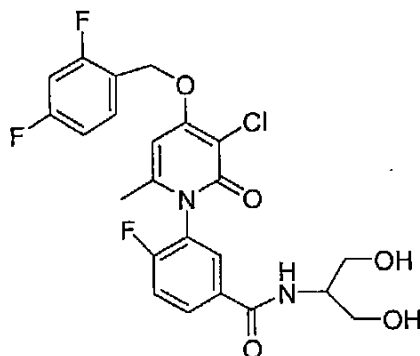
20 Preparation of 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride



A 100 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with the product from step 1 (1.5 g, 3.5 mmol), $\text{BH}_3 \cdot \text{THF}$ complex (7.4 mL, 7.4 mmol), and tetrahydrofuran (15 mL). The mixture was refluxed for 6 h, allowed to cool to room temperature and quenched with HCl 6N. The organics were evaporated and the remaining aqueous solution was saturated with NaOH 2.5N and extracted with dichloromethane. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. HCl 6N was added, and concentrated in vacuo. ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ 8.2 (m, 1H), 7.6 (m, 1H), 7.5 (m, 1H), 7.3 (t, $J = 9.8$ Hz, 1H), 7.16 (t, $J = 8.6$ Hz, 1H) 6.78 (s, 1H), 5.36 (s, 2H), 4.05 (d, $J = 5.8$ Hz, 2H), 2 (s, 3H) ppm. ES-HRMS m/z 409.0940 ($M+H$ calcd for $\text{C}_{20}\text{H}_{17}\text{ClF}_3\text{N}_2\text{O}_2$ requires 409.0925).

Example 524

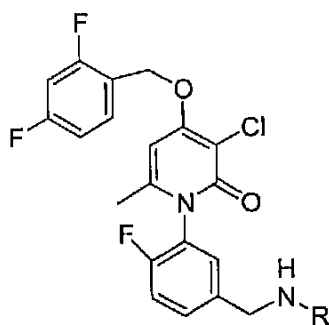
3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide



Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-[2-hydroxy-1-(hydroxymethyl)ethyl]benzamide

The title compound was prepared essentially as in Example 521. ¹H NMR (400 MHz, CD₃OD) δ 8.1 (m, 1H), 7.8 (dd, J = 2.3 and 5.1 Hz, 1H), 7.6 (q, J = 7.4 and 7.0 Hz, 1H), 7.41 (t, J = 8.9 Hz, 1H), 7.04 (m, 2H) 6.7 (s, 1H), 5.36 (s, 2H), 4.1 (t, J = 5.8 Hz, 1H), 3.7 (d, J = 5.1 Hz, 4H) 2.1 (s, 3H) ppm. ES-HRMS m/z 497. 1045 (M+H calcd for C₂₃H₂₁ClF₃N₂O₅ requires 497.1086).

Examples 525-528



The compounds of Examples 525-528 are prepared by derivitization of Example 523. The analytical data are shown below.

Ex. No.	R	MF	M+H	ESHRMS
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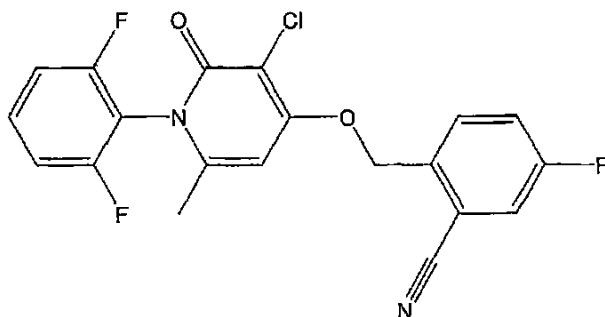
			Requires	m/z
Ex. 525	-C(O)CH ₃	C ₂₂ H ₁₈ ClF ₃ N ₂ O ₃	451.1031	451.1010
Ex. 526	-C(O)CH ₂ OCH ₃	C ₂₃ H ₂₀ ClF ₃ N ₂ O ₄	481.1136	481.1132
Ex. 527	-SO ₂ CH ₃	C ₂₁ H ₁₈ ClF ₃ N ₂ O ₄ S	487.0701	487.0679
Ex. 528	-C(O)NH ₂	C ₂₁ H ₁₆ ClF ₃ N ₃ O ₃	452.0983	452.0987

NMR characterization of compounds of Examples 525-528

Ex.No.	NMR Data
525	¹ H NMR (400 MHz, CD ₃ OD) δ 7.6 (q, J = 7.8 and 7.0 Hz, 1H), 7.5 (m, 1H), 7.3 (t, J = 9.0 Hz, 1H), 7.2 (dd, J = 1.9 and 5.1 Hz, 1H), 7.05 (m, 2H), 6.65 (s, 1H), 5.36 (s, 2H), 4.39 (s, 2H), 2.1 (s, 3H), 1.98 (s, 3H) ppm
526	¹ H NMR (400 MHz, CD ₃ Cl ₃) δ 7.45 (q, J = 8.6 and 6.2 Hz, 1H), 7.3 (m, 1H), 7.1 (m, 2H), 6.85 (q, J = 6.5 and 1.9 Hz, 1H), 6.78 (td, J = 2.7 and 7.8 Hz, 1H), 6.2 (s, 1H), 5.2 (s, 2H), 4.39 (d, J = 6.2 Hz, 2H), 4.0 (s, 3H) 2.3 (s, 2H), 2.0 (s, 3H), 1.98 (s, 3H) ppm
527	¹ H NMR (400 MHz, CD ₃ OD) δ 7.49 (q, J = 8.2 and 6.3 Hz, 1H), 7.33 (m, 1H), 7.23 (m, 1H), 7.1 (t, J = 8.9, 1H), 6.9 (td, J = 0.78 and 6.6 Hz, 1H), 6.8 (td, J = 2.7 and 6.25 Hz, 1H), 6.2 (s, 1H), 5.2 (s, 2H), 4.2 (s, 2H), 2.8 (s, 3H) 2.0 (s, 3H) ppm
528	¹ H NMR (400 MHz, (CD ₃) ₂ SO) δ 7.61 (q, J = 8.9 and 6.6 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.3 (d, J = 10.2 Hz, 1H) 7.21 (d, J = 7.4 Hz, 1H), 7.1 (t, J = 8.6 Hz, 1H), 6.71 (s, 1H), 6.5 (t, J = 5.8 Hz, 1H), 5.56 (s, 2H), 5.3 (s, 2H), 4.18 (d, J = 6.25 Hz, 2H), 3.61 (s, 1H), 1.98 (s, 3H) ppm

5

Example 529



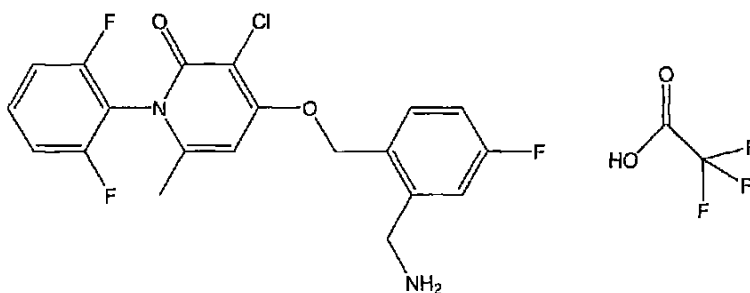
2-([3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy)methyl)-5-fluorobenzonitrile

10

2-(bromomethyl)-5-fluorobenzonitrile (3.47 g, 16.2 mmol), 3-chloro-1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (3.15 g, 11.6 mmol), K₂CO₃ (2.56 g, 18.6 mmol), and 18-crown-6 (0.15 g) were dissolved in N,N-dimethylacetamide (25 mL). Reaction mixture stirred on 60°C oil bath for 4 hours. Solvent removed by distillation. Reaction neutralized with 5% citric acid. The solid product was washed with hexane followed by 30% EtOAc/hexane. Filtered a brown solid (5.2 g, 79% yield).

¹H NMR (CD₃OD / 400MHz) δ 7.82 (m, 2H), 7.61 (m, 4H), 6.75 (s, 1H), 5.49 (s, 2H), 2.13 (s, 3H). ESHRMS m/z 405.0616 (M+H C₂₀H₁₃ClF₃N₂O₂ requires 405.0612).

Example 530



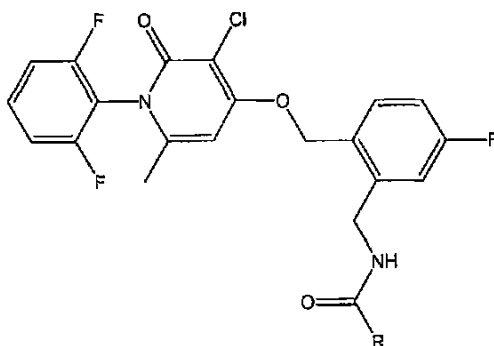
4-([2-(aminomethyl)-4-fluorobenzyl]oxy)-3-chloro-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one trifluoroacetate

BH₃THF (17.8 mL, 17.8 mmol) was added dropwise to a chilled (0°C) solution of 2-([3-chloro-1-(2,6-difluorophenyl)-6-methyl-2-oxo-1,2-dihydropyridin-4-yl]oxy)methyl)-5-fluorobenzonitrile (3.61 g, 8.92 mmol) in THF (30 mL). Following the addition, the reaction was heated at 60°C for 1.5 hours. The reaction was quenched with MeOH, the solvent evaporated, and the crude product purified by prep HPLC. The product was isolated by freeze-drying and evaporation of the solvent to give a white solid (1.52 g, 32.6%). ¹H NMR (CD₃OD/

400MHz) δ 7.62 (m, 2H), 7.32 (m, 1H), 7.25 (tr, 2H, $J = 8.00$ Hz), 7.18 (m, 1H), 6.78 (s, 1H), 5.43 (s, 1H), 4.22 (s, 1H), 2.14 (s, 3H). ESHRMS m/z 409.0900 ($M+H$ $C_{20}H_{17}N_2O_2F_3Cl$ requires 409.0925).

5

Examples 531-551



The compounds of Examples 531-551 are prepared by derivitization
10 of Example 530. The analytical data are shown below.

Compound No.	R	MF	M+H Requires	ESHRMS m/z
Ex. 531	-OCH ₃	C ₂₂ H ₁₈ ClF ₃ N ₂ O ₄	467.0980	467.0985
Ex. 532	-CF ₃	C ₂₂ H ₁₅ ClF ₆ N ₂ O ₃	505.0748	505.0754
Ex. 533	-O-isopropyl	C ₂₄ H ₂₂ ClF ₃ N ₂ O ₄	495.1293	495.1304
Ex. 534	-NH-CH ₂ CH ₃	C ₂₃ H ₂₁ ClF ₃ N ₃ O ₃	480.1296	480.1277
Ex. 535	-O-tetrahydrofuran-3-yl	C ₂₅ H ₂₂ ClF ₃ N ₂ O ₅	523.1242	523.1282
Ex. 536	-O-propyl	C ₂₄ H ₂₂ ClF ₃ N ₂ O ₄	495.1293	495.1338
Ex. 537	-O-CH ₂ CH=CH ₂	C ₂₄ H ₂₀ ClF ₃ N ₂ O ₄	493.1136	493.1116
Ex. 538	-O-CH ₂ C≡CH	C ₂₄ H ₁₈ ClF ₃ N ₂ O ₄	491.0980	491.0961
Ex. 539	-O-tButyl	C ₂₅ H ₂₄ ClF ₃ N ₂ O ₄	509.1449	509.1436
Ex. 540	-NH-tButyl	C ₂₅ H ₂₅ ClF ₃ N ₃ O ₃	508.1609	508.1574
EX. 541	-SO ₂ CH ₂ CH ₂ CH ₃	C ₂₃ H ₂₂ ClF ₃ N ₂ O ₄ S	515.1014	515.0979

Ex. 542	-SO ₂ CH ₂ CH ₃			
Ex. 543	-NH-isopropyl	C ₂₄ H ₂₃ ClF ₃ N ₃ O ₃	494.1453	494.1456
Ex. 544	-CH ₂ OCH ₃	C ₂₃ H ₂₀ ClF ₃ N ₂ O ₄	481.1136	481.1174
Ex. 545	-NHCH ₃	C ₂₂ H ₂₀ ClF ₃ N ₃ O ₃	466.1140	466.1141
Ex. 546	-N(CH ₃) (tButyl)	C ₂₆ H ₂₇ ClF ₃ N ₃ O ₃	522.1766	522.1737
Ex. 547	-NH(cyclopropyl)	C ₂₄ H ₂₁ ClF ₃ N ₃ O ₃	492.1296	492.1285
Ex. 548	-NHCH ₂ CF ₃	C ₂₃ H ₁₇ ClF ₆ N ₃ O ₃	534.1014	534.1005
Ex. 549	NHCH ₂ (cyclopropyl)	C ₂₅ H ₂₃ ClF ₃ N ₃ O ₃	506.1453	506.1432
Ex. 550	-NHCH ₂ (tButyl)	C ₂₆ H ₂₇ ClF ₃ N ₃ O ₃	522.1766	522.1740
Ex. 551	-N(CH ₃) ₂	C ₂₃ H ₂₂ ClF ₃ N ₃ O ₃	480.1296	480.1307

NMR characterization of compounds of Examples 531-551

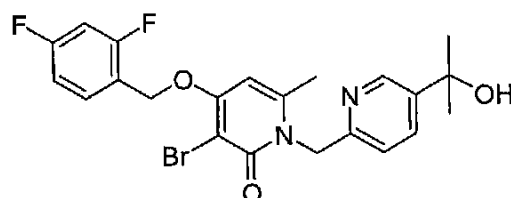
Ex. No.	NMR data
531	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 8.00Hz), 7.14 (m, 1H), 7.05 (m, 1H), 6.74 (s, 1H), 5.40 (s, 2H), 4.42 (s, 2H), 3.63 (s, 3H), 2.12 (s, 3H)
532	¹ H NMR (CD ₃ OD / 400MHz) δ7.59 (m, 2H), 7.24 (t, 2H, J = 8.00 Hz), 7.11 (m, 2H), 6.73 (s, 1H), 5.43 (s, 2H), 4.62 (s, 2H), 2.12 (s, 3H)
533	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 7.60 Hz), 7.13 (m, 1H), 7.05 (m, 1H), 6.74 (s, 1H), 5.40 (s, 2H), 4.81 (m, 1H), 4.41 (s, 2H), 2.12 (s, 3H), 1.21 (d, 6H, J = 6.00 Hz)
534	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 0.80 Hz), 7.13 (m, 1H), 7.03 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.44 (s, 2H), 3.12 (q, 2H, J = 7.20 Hz), 2.12 (s, 3H), 1.08 (t, 3H, J = 7.20 Hz)
535	¹ H NMR (CD ₃ OD / 300MHz) δ7.62 (m, 1H), 7.54 (m, 1H), 7.25 (t, 2H, J = 8.4 Hz), 7.15 (m, 1H), 7.07 (m, 1H), 6.75 (s, 1H), 5.41 (s, 2H), 5.15 (s br, 1H), 4.44 (s, 2H), 3.82 (m, 4H), 2.13 (s, 4H), 2.03 (s br, 1H)
536	¹ H NMR (CD ₃ OD / 300MHz) δ7.62 (m, 1H), 7.54 (m, 1H), 7.25 (t, 2H, J = 8.1 Hz), 7.15 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 4.43 (s, 2H), 3.98 (t, 2H, J = 6.6 Hz), 2.13 (s, 3H), 1.63 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz)
537	¹ H NMR (CD ₃ OD / 300MHz) δ7.62 (m, 1H), 7.54 (m, 1H), 7.25 (t, 2H, J = 8.4 Hz), 7.14 (m, 1H), 7.07 (m, 1H), 6.74 (s, 1H), 5.92 (m br, 1H), 5.41 (s, 2H), 5.29 (d, 1H, J = 17.7 Hz), 5.17 (d, 1H, J = 10.5 Hz), 4.63 (s, 1H), 4.53 (d, 2H, J = 5.4 Hz), 4.44 (s, 2H), 2.13 (s, 3H)
538	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 7.6 Hz), 7.14 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 4.65 (d, 2H, J = 2.4 Hz), 4.44 (s, 2H), 2.86 (t, 1H, J =

	2.4 Hz), 2.12 (s, 3H)
539	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (tr, 2H, J = 8.40), 7.12 (m, 1H), 7.05 (m, 1H), 6.74 (s, 1H), 5.39 (s, 2H), 4.36 (s, 2H), 2.12 (s, 3H), 1.43 (s, 9H)
540	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (tr, 2H, J = 8.00 Hz), 7.12 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.37 (s, 2H), 4.39 (s, 2H), 2.12 (s, 3H), 1.28 (s, 9H)
541	¹ H NMR (CD ₃ OD / 300MHz) δ7.59 (m, 2H), 7.26 (m, 3H), 7.11 (m, 1H), 6.75 (s, 1H), 5.46 (s, 2H), 4.40 (s, 2H), 3.02 (m, 2H), 2.12 (s, 3H), 1.80 (m, 2H), 1.03 (tr, 3H, J = 7.50 MHz)
542	¹ H NMR (CD ₃ OD / 400MHz) δ7.58 (m, 2H), 7.26 (m, 3H), 7.10 (m, 1H), 6.74 (s, 1H), 5.45 (s, 2H), 4.39 (s, 2H), 3.06 (q, 2H, J = 7.60 Hz), 2.11 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz)
543	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 8.40 Hz), 7.12 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.44 (s, 2H), 3.77 (m, 1H), 2.12 (s, 3H), 1.10 (d, 6H, J = 6.40 Hz)
544	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.54 (m, 1H), 7.24 (t, 2H, J = 7.6 Hz), 7.15 (m, 1H), 7.06 (m, 1H), 6.74 (s, 1H), 5.43 (s, 2H), 4.55 (s, 2H), 3.92 (s, 2H), 3.40 (s, 3H), 2.12 (s, 3H)
545	¹ H NMR (CD ₃ OD / 300MHz) δ7.63 (m, 1H), 7.54 (m, 1H), 7.26 (t, 2H, J = 8.7 Hz), 7.15 (m, 1H), 7.05 (m, 1H), 6.75 (s, 1H), 5.42 (s, 2H), 4.47 (s, 2H), 2.70 (s, 3H), 2.14 (s, 3H)
546	¹ H NMR (CD ₃ OD / 300MHz) δ7.63 (m, 1H), 7.53 (m, 1H), 7.25 (t, 2H, J = 9.0 Hz), 7.14 (m, 1H), 7.04 (m, 1H), 6.76 (s, 1H), 5.41 (s, 2H), 4.44 (s, 2H), 2.90 (s, 3H), 2.13 (s, 3H), 1.39 (s, 9H)
547	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 7.6 Hz), 7.14 (m, 1H), 7.03 (m, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 4.47 (s, 2H), 2.46 (m, 1H), 2.12 (s, 3H), 0.68 (q, 2H, J = 5.2 Hz), 0.46 (m, 2H)
548	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 8.0 Hz), 7.12 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.47 (s, 2H), 3.79 (q, 2H, J = 9.6 Hz), 2.12 (s, 3H)
549	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.52 (m, 1H), 7.24 (t, 2H, J = 8.4 Hz), 7.14 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.45 (s, 2H), 2.96 (d, 2H, J = 6.8 Hz), 2.12 (s, 3H), 0.93 (m, 1H), 0.44 (m, 2H), 0.16 (q, 2H, J = 4.8 Hz)
550	¹ H NMR (CD ₃ OD / 400MHz) δ7.61 (m, 1H), 7.53 (m, 1H), 7.24 (t, 2H, J = 8.0 Hz), 7.14 (m, 1H), 7.04 (m, 1H), 6.73 (s, 1H), 5.39 (s, 2H), 4.46 (s, 2H), 2.92 (d, 2H, J = 4.8 Hz), 2.12 (s, 3H), 0.87 (s, 9H)
551	¹ H NMR (CD ₃ OD / 300MHz) δ7.62 (m, 1H), 7.52 (m, 1H), 7.25 (t, 2H, J = 8.7 Hz), 7.15 (m, 1H), 7.04 (m, 1H), 6.75 (s, 1H), 5.42 (s, 2H), 4.48 (s, 2H), 2.90 (s, 6H), 2.14 (s, 3H)

¹H NMR (CD₃OD / 400MHz) δ7.58 (m, 2H), 7.26 (m, 3H), 7.10 (m, 1H), 6.74 (s, 1H), 5.45 (s, 2H), 4.39 (s, 2H), 3.06 (q, 2H, J = 7.60 Hz), 2.11 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz) ¹H NMR (CD₃OD / 300MHz) δ7.63 (m, 1H), 7.54 (m, 1H), 7.26 (t, 2H, J =

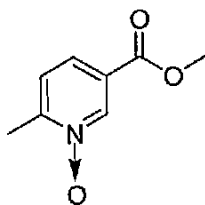
8.7 Hz), 7.15 (m, 1H), 7.05 (m, 1H), 6.75 (s, 1H), 5.42 (s, 2H), 4.47 (s, 2H), 2.70 (s, 3H), 2.14 (s, 3H). ESHRMS m/z 466.1141 (M+H C₂₂H₂₀ClF₃N₃O₃ requires 466.1140).

5 Example 552



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-[(5-(1-hydroxy-1-methylethyl)pyridin-2-yl)methyl]-6-methylpyridin-2(1H)-one

Step 1: Preparation of methyl 6-methylnicotinate 1-oxide .

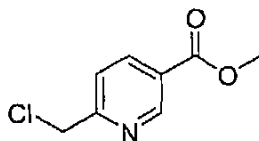


15

Methyl 6-methylnicotinate (6.0 g, 39.7 mmol) was added into dichloromethane (100 mL) in the round bottom flask under nitrogen. 3-chloroperoxybenzoic acid (10.0 g, 57.9 mmol) was then added into the flask and stirred for 5 hour. Saturated sodium bicarbonate solution (100 ml) was added into the reaction and the mixture was transferred to separatory funnel. Additional 200mL of dichloromethane was added into the funnel and obtained the organic layer. The organic layer was washed with water (150 mL) and dried over anhydrous magnesium sulfate. The resulting solution was evaporated to yield white solid (6 g, 90 %). LC/MS, t_r = 0.33 minutes (5 to 95%

acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 168 (M+H). ES-HRMS m/z 168.0628 (M+H calcd for C₈H₁₀NO₃ requires 168.0655).

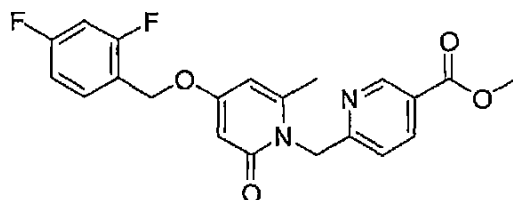
5 Step 2: Preparation of methyl 6-(chloromethyl)nicotinate .



Methyl 6-methylnicotinate 1-oxide (from Step 1) (6.0 g, 35.9 mmol) was added into the p-toluenesulfonyl chloride (10 g, 52.4 mmol) in 100 mL of 1,4- dioxane. The mixture was heated to reflux for 20 hours. Saturated sodium bicarbonate solution (200 ml) was added into the reaction and the mixture was transferred to separatory funnel. The compound was extracted using ethyl acetate (300ml x 2) and the combined ethyl acetate solution was dried over magnesium sulfate and evaporated to black solid (5.2 g, 78%). LC/MS, t_r = 1.52 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 186 (M+H). ES-HRMS m/z 186.0314 (M+H calcd for C₈H₉ClNO₂ requires 186.0316).

20

Step 3: Preparation of methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate .



25 Methyl 6-(chloromethyl)nicotinate (from step 2). (2 g, 10.8 mmol) was added into 4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one in 20 mL of dimethyl formamide followed by addition of cesium carbonate (5g, 15.3 mmol). The

mixture was heated to 100 C for 20 hours. It was cooled to room temperature and added 400 mL of water. Brown precipitate came out of from solution. It was filtered and rinsed with water (200 mL x 3) and dried to obtain 4 g of solid. The product was purified using a Gilson Reversed Phase preparative chromatography to obtain white solid (1.4 g, 32%). ¹H NMR (400 MHz, CDCl₃) δ 9.09 (d, J = 1.48 Hz, 1H), 8.19 (dd, J = 6.04, 2.15 Hz, 1H), 7.37 (app q, J = 8.32 Hz, 1H), 7.25 (d, J = 8.33 Hz, 1H), 6.84 (m, 2H), 5.94 (d, J = 2.82 Hz, 1H), 5.83 (d, J = 2.15 Hz, 1H), 5.36 (s, 2H), 4.97 (s, 2H), 3.90 (s, 3H), 2.27 (s, 3H); LC/MS, t_r = 2.30 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 401 (M+H). ES-HRMS m/z 401.1307 (M+H calcd for C₂₁H₁₉F₂N₂O₄ requires 401.1307).

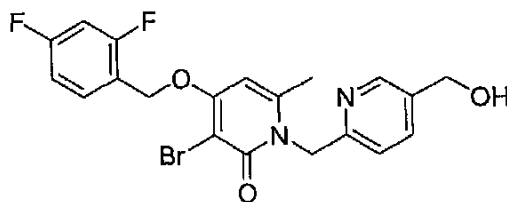
Step 4: Preparation of the title compound .

3 molar solution of methyl magnesium bromide in ether (5mL, 15mmol) was added into 5 ml of anhydrous tetrahydrofuran in the round bottom flaks under nitrogen. The mixture was cooled to 0°C. Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (from Step 3) (300mg, 0.75mmol) was dissolved in 5 ml of anhydrous tetrahydrofuran in dropper funnel and the solution was slowly added into cold methyl magnesium bromide solution in the round bottom flask. After the addition, the mixture was continue stirring at 0 C for 30 minute and cold solution of saturated ammonium chloride (100 ml) was added slowly into the reaction mixture. The mixture was transferred to separatory funnel and the product was extracted with ethyl acetate (200ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. The resulting residue (220 mg) was added into 10 ml of dichloromethane

followed by addition of N-bromo succinimide (100 mg, 0.56 mmol). The solution was stirred at room temperature for 3 hours. Saturated sodium bicarbonate solution (100 ml) was added into the reaction mixture and it was transferred to separatory funnel. The product was extracted with ethyl acetate (200ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness.

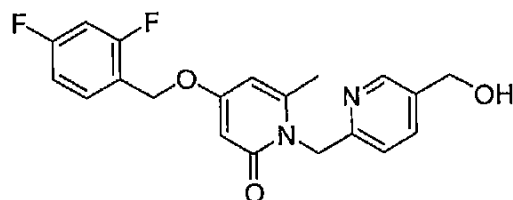
¹H NMR (400 MHz, CDCl₃) δ 8.61 (d, J = 1.88 Hz, 1H), 7.73 (dd, J = 5.77, 2.42 Hz, 1H), 7.55 (app q, J = 6.31 Hz, 1H), 7.30 (d, J = 8.19 Hz, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 6.00 (s, 1H), 5.37 (s, 2H), 5.19 (s, 2H), 2.48 (s, 3H), 1.56 (s, 6H); LC/MS, t_r = 2.29 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 479 (M+H). ES-HRMS m/z 479.0791 (M+H calcd for C₂₂H₂₂BrF₂N₂O₃ requires 479.0776).

Example 553



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one



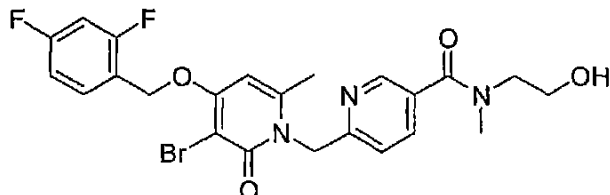
Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (from preparation of step 3) (350 mg, 0.87 mmol) was added into anhydrous
5 tetrahydrofuran (15 ml) and the solution was cooled to -78 C. Into the cold solution, was added lithium aluminum hydride (100 mg, 2.6 mmol). After the addition, the reaction mixture was warm to 0 C and continue stirring for one additional hour. Potassium hydrogen sulfate (1 N solution, 150 ml) was added
10 slowly into the reaction mixture to quench the reaction. The resulting mixture was transferred to a separatory funnel and the product was extracted with ethyl acetate (200ml x 2). The combine ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. LC/MS, t_r = 1.88
15 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 373 (M+H)

Step 2: Preparation of the title compound .

4-[(2,4-difluorobenzyl)oxy]-1-{[5-(hydroxymethyl)pyridin-2-yl]methyl}-6-methylpyridin-2(1H)-one (from step 1). (230 mg,
20 0.62 mmol) was added into 10 ml of dichloromethane followed by addition of N-bromo succinimide (110 mg, 0.62 mmol). The solution was stirred at room temperature for 3 hours. Saturated sodium bicarbonate solution (100 ml) was added into
25 the reaction mixture and it was transferred to a separatory funnel. The product was extracted with ethyl acetate (200ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. ^1H NMR (400 MHz, CDCl_3) δ 8.47 (app s, 1H), 7.64 (dd, J = 5.77, 2.29

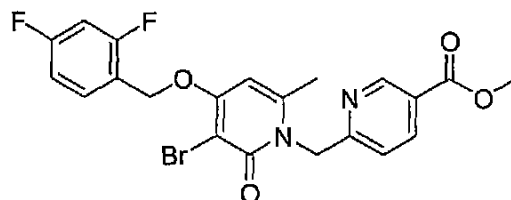
Hz, 1H), 7.55 (app q, $J = 6.45$ Hz, 1H), 7.33 (d, $J = 6.05$ Hz, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 6.00 (s, 1H), 5.39 (s, 2H), 5.19 (s, 2H), 4.68 (s, 2H), 2.46 (s, 3H); LC/MS, $t_r = 2.01$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 451 (M+H)

Example 554



6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-
10 1(2H)-yl]methyl}-N-(2-hydroxyethyl)-N-methylnicotinamide

Step 1: Preparation of methyl 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate .

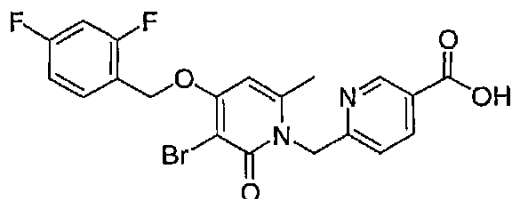


15

Methyl 6-{[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (350 mg, 0.87 mmol) (1.0 g, 2.5 mmol) was added into 150 ml of dichloromethane followed by addition of N-bromo succinimide (500 mg, 2.8 mmol). The
20 solution was stirred at room temperature for 3 hours. Saturated sodium bicarbonate solution (300 ml) was added into the reaction mixture and it was transferred to a separatory funnel. The product was extracted with ethyl acetate (500ml x2). The combined ethyl acetate solution was dried over
25 anhydrous magnesium sulfate and evaporated to dryness. ^1H NMR (400 MHz, CDCl_3) δ 9.08 (app d, $J = 2.15$ Hz, 1H), 8.21 (dd, $J =$

6.04, 2.15 Hz, 1H), 7.55 (app qt, $J = 6.31$ Hz, 1H), 7.41 (d, $J = 6.31$ Hz, 1H), 6.91 (m, 1H), 6.84 (m, 1H), 6.02 (s, 1H), 5.42 (s, 2H), 5.19 (s, 2H), 3.91 (s, 3H), 2.45 (s, 3H); LC/MS, $t_r = 2.85$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 479 (M+H). ES-HRMS m/z 479.0415 (M+H calcd for $C_{21}H_{18}BrF_2N_2O_4$ requires 479.0413).

Step 2: Preparation of 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinic acid .



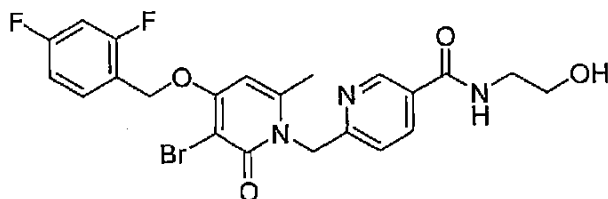
Methyl 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinate (from step 1) (1.0 g, 2.1 mmol) was added into the mixture of 100 ml tetrahydrofuran and 10 ml of methanol followed by addition of 2.5 N sodium hydroxide(0.85 ml, 2.1 mmol). The solution was heated to 50 C for 2 hours. After the solution was cooled to room temperature and evaporate to completely dried residue. The residue was added into 50 ml of tetrahydrofuran and 4 N HCl in 1,4-dioxane (0.52 ml, 2.1 mmol) and stirred the mixture for 30 minute. The mixture was evaporate to dryness. The residue was added 20 ml water and the aqueous solution was neutralized to exactly ph 7 by addition of saturated sodium bicarbonate solution drop wise. The resulting heterogeneous mixture was left standed for 20 hours. Filtered, rinsed with water (30 ml x 3) and dried over high vacuum oven to afford white solid(950 mg, 97%).

^1H NMR (400 MHz, CDCl_3 and CD_3OD) δ 8.98 (app br s, 1H), 8.15 (dd, $J = 6.17, 2.02$ Hz, 1H), 7.45 (app q, $J = 6.58$ Hz, 1H), 7.21 (d, $J = 8.19$ Hz, 1H), 6.84 (m, 1H), 6.76 (m, 1H), 6.04 (s, 1H), 5.35 (s, 2H), 5.12 (s, 2H), 2.32 (s, 3H); LC/MS, $t_r =$ 2.48 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 465 (M+H). ES-HRMS m/z 465.0254 (M+H calcd for $\text{C}_{20}\text{H}_{16}\text{BrF}_2\text{N}_2\text{O}_4$ requires 465.0256).

10 Step 3: Preparation of the title compound .

6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}nicotinic acid (from step 2) (230 mg, 0.5 mmol) was added into the 1-hydroxybenzotriazole (101mg, 0.75 mmol) in 5 ml of N,N-dimethylformamide. 4 -methyl morpholine (0.16 ml, 1.5 mmol) was added into the mixture followed by addition of 1-(3-(dimethylamino) propyl-3-ethylcarbodiimide hydrochloride (143 mg, 0.75 mmol). Stirred the mixture for 30 minute to become homogenous solution. To that homogenous solution, was added 2-(methylamino) ethanol(0.06 ml, 0.75 mmol) and the mixture was stirred for 20 hours. Water (150 ml) was added into the reaction mixture and the product was extracted using ethyl acetate (400ml x2). The combined ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. ^1H NMR (400 MHz, DMSO- d_6) δ 8.47 (app br s, 1H), 7.80 (br d, $J = 7.92$ Hz, 1H), 7.64 (app q, $J = 6.58$ Hz, 1H), 7.30 (m, 2H), 7.15 (m, 1H), 6.56 (s, 1H), 5.39 (s, 2H), 5.28 (s, 2H), 3.46 (m, 2H), 3.23 (m, 2H) 2.93 (m, 3H), 2.36 (s, 3H); LC/MS, $t_r = 2.29$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-HRMS m/z 522.0850 (M+H calcd for $\text{C}_{23}\text{H}_{23}\text{BrF}_2\text{N}_3\text{O}_4$ requires 522.0835).

Example 555

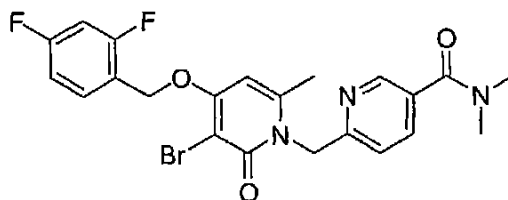


6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N-(2-hydroxyethyl)nicotinamide

5

Following the method of Example 554 (step 3) and substituting 2-(methyamino)ethanol for the ethanolamine obtained the title compound as a white solid (79% yield). ¹H NMR (400 MHz, CD₃OD) δ 8.93 (d, J = 2.01 Hz, 1H), 8.21 (dd, J = 6.04, 2.21 Hz, 1H), 7.67 (app q, J = 6.44 Hz, 1H), 7.39 (d, J = 8.06 Hz, 1H), 7.08 (m, 2H), 6.58 (s, 1H), 5.55 (s, 2H), 5.35 (s, 2H), 3.74 (app t, J = 5.73Hz, 2H), 3.53 (app t, J = 5.73Hz, 2H), 2.49 (s, 3H); LC/MS, t_r = 2.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 15 254 nm, at 50°C). ES-HRMS m/z 508.0673 (M+H calcd for C₂₂H₂₁BrF₂N₃O₄ requires 508.0678).

Example 556

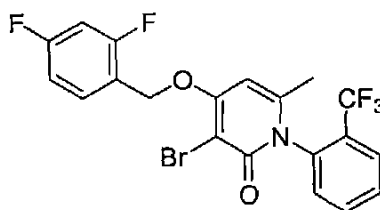


20 6-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}-N,N-dimethylnicotinamide

Following the method of Example 554 (step 3) and substituting dimethylamine for the ethanolamine obtained the title compound 25 as a white solid (75% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.55 (d, J = 1.62 Hz, 1H), 7.68 (dd, J = 5.77, 2.15 Hz, 1H), 7.55

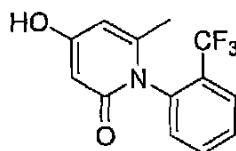
(app q, $J = 6.45$ Hz, 1H), 7.37 (d, $J = 8.06$ Hz, 1H), 6.93 (m, 1H), 6.84 (m, 1H), 6.02 (s, 1H), 5.40 (s, 2H), 5.20 (s, 2H), 3.09 (s, 3H), 2.97 (s, 3H), 2.45 (s, 3H); LC/MS, $t_r = 2.45$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-HRMS m/z 492.0710 ($M+H$ calcd for $C_{22}H_{21}BrF_2N_3O_3$ requires 492.0729).

Example 557



10 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one

Step 1: Preparation of 4-hydroxy-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one .



15

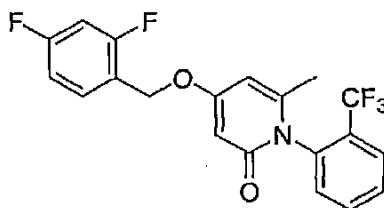
4-hydroxy-6-methyl-2-pyrone (10g, 79.3 mmol) was added into the 2-(trifluoromethyl) aniline (14 ml, 111.3 mmol) in 10 ml of 1,2-dichlorobenzene in a round bottom flask. The mixture was then placed in a pre-heated oil bath at 165 C.

20 After 30 minute of heating, the mixture was cooled to room temperature and added 250 ml of saturated sodium bicarbonate solution. The mixture was stirred at room temperature for 15 minutes and transferred to a separatory funnel. Ethyl acetate (300ml) was added into the separatory funnel and partitions the layers. The aqueous layer was obtained and the organic layer was added 200 ml of saturated sodium bicarbonate solution. The aqueous layer was obtained again and the

25

combined aqueous solution was neutralized with HCl solution. Upon neutralization, white solid precipitated out of the solution. Filtered the solid, rinsed with water (100 ml x5) and dried over high vacuum oven to obtain the white solid (7.5 g, 35.5%). LC/MS, t_r = 1.77 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 270 (M+H).

Step 2: Preparation of 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one .



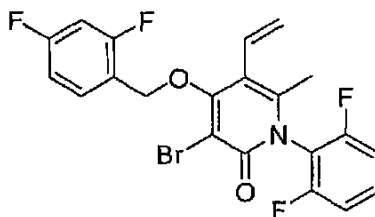
4-hydroxy-6-methyl-1-[2-(trifluoromethyl)phenyl]pyridin-2(1H)-one (from Step 1) (7.3 g, 27.1 mmol) was added into 3,4-difluorobenzyl bromide (5.5 g, 26.5 mmol) in 60 ml of dimethyl formamide. The mixture was cooled to 0 C and cesium carbonate (20g, 61.3 mmol) was added into the mixture. After the addition, the mixture was warmed to room temperature and stirred for 4 hours. Water (500ml) was added into the reaction mixture. Yellow solid came out of solution. Filtered and rinsed with water (200ml x 2) to obtain the yellow solid. Dissolved the solid in ethyl acetate (500 ml) and water (300 ml) and transfer to a separatory funnel and obtained the organic layer. The organic layer was washed again with water (200ml) and dried over anhydrous magnesium sulfate. The organic solution was evaporated to dryness. ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 7.65 Hz, 1H), 7.7 (t, J = 7.52 Hz, 1H), 7.58 (t, J = 7.65 Hz, 1H), 7.42 (q, J = 6.45 Hz,

1H), 7.27 (d, J = 7.78 Hz, 2H), 6.89 (m, 2H), 5.95 (app d, J = 2.42Hz, 1H), 5.90 (app d, J = 2.42Hz, 1H), 5.01 (app d, J = 2.94 Hz, 2H), 1.86 (s, 3H); LC/MS, t_r = 2.74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection
5 254 nm, at 50°C). ES-MS m/z 396 (M+H)

Step 3: Preparation of the title compound.

N-bromosuccinimide (0.24g, 1.36 mmol) was added into 4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-[2-
10 (trifluoromethyl)phenyl]pyridin-2(1H)-one (0.54g, 1.36 mmol) in 20 ml of dichloromethane. The mixture was stirred at room temperature for 2 hours. Saturated sodium bicarbonate solution (150 ml) was added into the reaction mixture and the combine solution was transferred to a separatory funnel. The
15 product was extracted with ethyl acetate (250ml). The ethyl acetate solution was dried over anhydrous magnesium sulfate and evaporated to dryness. ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 7.25 Hz, 1H), 7.7 (app t, J = 7.66 Hz, 1H), 7.60 (m, 2H), 7.26 (s, 1H), 6.97 (m, 1H), 6.87 (m, 1H), 6.09 (s, 1H), 5.25
20 (app d, J = 3.35Hz, 2H), 1.94 (s, 3H); LC/MS, t_r = 2.84 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-HRMS m/z 474.0113 (M+H calcd for $\text{C}_{20}\text{H}_{14}\text{BrF}_5\text{NO}_2$ requires 474.0123).

25 Example 558

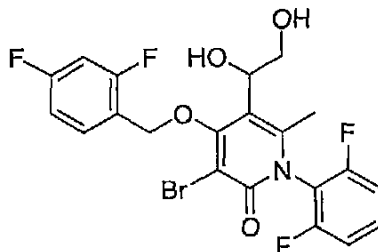


3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.00 g, 1.76 mmol) in anhydrous THF (12 mL) was added, sequentially, tributyl(vinyl)tin (1.21 g, 3.81 mmol) and tetrakis(triphenylphosphine)palladium (236 mg, 0.204 mmol) under an argon stream. The reaction vessel was then equipped with a reflux condenser and the reaction system purged with an argon flow. The resulting yellow solution was heated to 68 °C and stirred under a positive pressure of argon for 12.0 hours until complete disappearance of starting material by LCMS analysis. The reaction mixture was concentrated in vacuo and the resulting dark residue was subjected to SiO₂ chromatography with ethyl acetate/hexanes (3:7) to furnish a reddish solid. ¹H NMR (400 MHz, CDCl₃) δ 7.62 (app q, J = 7.8 Hz, 1H), 7.45 (app tt, J = 8.4, 6.2, 1H), 7.09 (app t, J = 8.8 Hz, 2H), 6.90 (app t, J = 8.0 Hz, 1H), 6.83 (app dt, J = 6.8, 2.5 Hz, 1H), 6.51 (dd, J = 17.7, 11.4 Hz, 1H), 5.53 (dd, J = 11.4, 1.5 Hz, 1H), 5.41 (dd, J = 17.8, 1.5 Hz, 1H), 5.09 (br s, 2H), 2.09 (s, 3H); LC/MS C-18 column, t_r = 3.20 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 468 (M+H). ES-HRMS m/z 468.0210 (M+H calcd for C₂₁H₁₅BrF₄NO₂ requires 468.0217).

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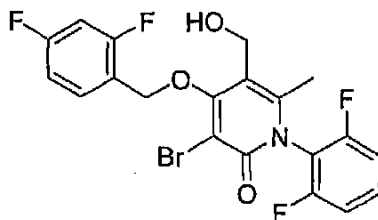
Example 560



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-6-methylpyridin-2(1H)-one

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one (0.970 g, 2.07 mmol) in water/acetone 1:3 (8.7 mL) was added, sequentially, osmium tetroxide (0.110 g, 0.433 mmol) and N-methyl morpholine oxide (1.32 g, 11.2 mmol). The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis, and the reaction was concentrated in vacuo. The resulting dark residue was subjected to SiO₂ chromatography with ethyl acetate/hexanes (3:7) to furnish a solid. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (app q, J = 8.2 Hz, 1H), 7.45 (ddd, J = 14.7, 8.5, 6.8 Hz, 1H), 7.08 (app t, J = 8.5 Hz, 2H), 6.94 (app t, J = 8.2 Hz, 1H), 6.88 (app t, J = 8.5 Hz, 1H), 5.31 (AB-q, J = 10.6 Hz, Δ = 38.3 Hz, 2H), 5.07 (dd, J = 9.1, 3.8 Hz, 1H), 3.83 (t, J = 10.8 Hz, 1H), 3.60 (dd, J = 11.4, 3.9 Hz, 1H), 2.94 (br s, 1H), 2.16 (s, 3H); LC/MS C-18 column, t_r = 2.26 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 502 (M+H). ES-HRMS m/z 502.0276 (M+H calcd for C₂₁H₁₇BrF₄NO₄ requires 502.0272).

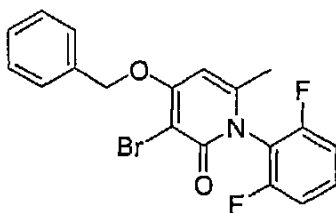
Example 561



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1H)-one

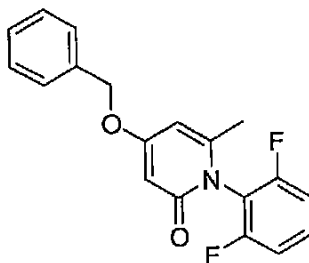
Step 1: To a -20°C solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde (0.659 g, 1.40 mmol) in methanol (10 mL) was added, portionwise, solid sodium borohydride (3.6 g, 96 mmol) over one hour until complete consumption of starting material by LCMS analysis. Next, the reaction mixture was diluted with 500 mL of ethyl acetate and washed with 3 X 200 mL of water. The resulting organic extract was Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 100 mL volume. The resulting liquid was diluted with hexanes (100 mL) to furnish an amorphous solid that was collected and dried at 1 mm Hg vacuum to furnish (620 mg, 94 %) of the desired product. ^1H NMR (400 MHz, d_4 -MeOH) δ 7.70 (app q, $J = 8.3$ Hz, 1H), 7.62 (app tt, $J = 10.4, 6.3$ Hz, 1H), 7.25 (app t, $J = 8.6$ Hz, 2H), 7.03 (app t, $J = 8.6$ Hz, 1H), 6.88 (app t, $J = 8.5$ Hz, 1H), 5.31 (s, 2H), 4.58 (s, 2H), 2.17 (s, 3H); LC/MS C-18 column, $t_r = 2.49$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 mL/min with detection 254 nm, at 50°C). ES-MS m/z 472 ($\text{M}+\text{H}$). ES-HRMS m/z 472.0152 ($\text{M}+\text{H}$ calcd for $\text{C}_{20}\text{H}_{15}\text{BrF}_4\text{NO}_3$ requires 472.0166).

Example 562



4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one

Step 1: Preparation of 4-(benzyloxy)-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one .

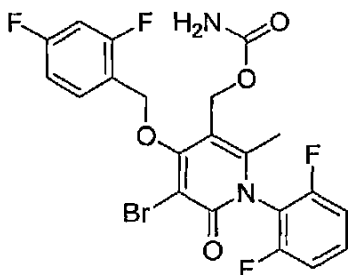


To a briskly stirred room temperature solution of 1-(2,6-difluorophenyl)-4-hydroxy-6-methylpyridin-2(1H)-one (1.43 g, 6.03 mmol) in dimethylformamide (4.6 mL) was added
5 sequentially K_2CO_3 (2.01 g, 14.5 mmol) and benzyl bromide (2.40 mL, 20.2 mmol). The resulting suspension was stirred for 6.5 hours until complete consumption of starting material by LCMS analysis. The reaction was then diluted with ethyl acetate (200 mL) and brine washed (3 X 200 mL). The resulting
10 organic extract was Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 100 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1.62 g, 82 %). 1H NMR (300 MHz, d_4 -MeOH) δ 7.62 (app
15 tt, J = 8.6, 6.4 Hz, 1H), 7.52-7.32 (m, 4H), 7.30-7.12 (m, 3H), 6.27 (d, J = 1.6 Hz, 1H), 6.04 (d, J = 2.6 Hz, 1H), 5.18 (s, 2H), 2.06 (s, 3H). LC/MS C-18 column, t_r = 2.51 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 mL/min with detection 254 nm, at 50°C). ES-MS m/z 328 ($M+H$). ES-HRMS m/z
20 328.1179 ($M+H$ calcd for $C_{19}H_{16}F_2NO_2$ requires 328.1144).

Step 2: To a room temperature solution of 4-(benzyloxy)-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (1.52 g, 4.64 mmol) in methylene chloride (15 mL) was added solid N-
25 bromosuccinimide (2.01 g, 11.3 mmol) and the resulting reddish solution was stirred for 4.0 hours. At this time the reaction was diluted with ethyl acetate (400 mL) and washed with sodium sulfite (5 % aqueous solution, 100 mL) and brine

(3 X 200 mL). The resulting organic extracts were Na₂SO₄ dried, filtered, and concentrated in vacuo to approximately 60 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1.70 g, 91 %). ¹H NMR (300 MHz, d₄-MeOH) δ 7.64 (app tt, J = 8.6, 6.4 Hz, 1H), 7.57 (br d, J = 7.1 Hz, 1H), 7.50-7.34 (m, 4H), 7.27 (app t, J = 8.0 Hz, 1H), 7.26-7.21 (m, 1H), 6.66 (s, 1H), 5.40 (s, 2H), 2.12 (s, 3H); LC/MS C-18 column, t_r = 2.63 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 406 (M+H). ES-HRMS m/z 406.0228 (M+H calcd for C₁₉H₁₅BrF₂NO₂ requires 406.0249).

Example 563

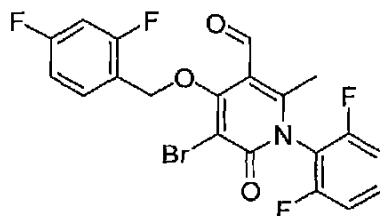


5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridin-3-yl methyl carbamate

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(hydroxymethyl)-6-methylpyridin-2(1H)-one (76.2 mg, 0.161mmol) in methylene chloride (0.4 mL) was added a solution of trichloroacetyl isocyanate (toluene, 0.60 M, 0.5 mL, 0.30 mmol). The resulting solution was stirred for one hour until complete consumption of starting material by LCMS analysis. The reaction mixture was then directly applied to Al₂O₃ (0.5 g of Broeckman-activity type I) and the slurry was matured for three hours. At this time, the Al₂O₃ plug was flushed with ethyl acetate/methanol

(95:5) and the resulting mother liquor was concentrated to a residue that was subjected to SiO₂ chromatography using ethyl acetate/hexanes (1:1) to furnish a white solid (71.0 mg, 85 %). ¹H NMR (400 MHz, d₄-MeOH) δ 7.71-7.59 (m, 2H), 7.26 (app t, J = 8.5 Hz, 2H), 7.02 (app t, J = 9.2 Hz, 2H), 5.32 (s, 2H), 5.02 (s, 2H), 2.15 (s, 3H); LC/MS C-18 column, t_r = 2.35 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 515 (M+H). ES-HRMS m/z 515.0188 (M+H calcd for C₂₁H₁₆BrF₄N₂O₄ requires 515.0224).

Example 564



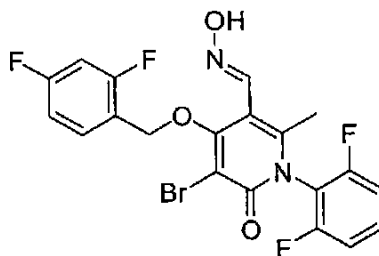
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5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde

Step 1: To a room temperature solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-(1,2-dihydroxyethyl)-6-methylpyridin-2(1H)-one (550 mg, 1.10 mmol) in toluene (10.0 mL) was added lead(IV) acetate (810 mg, 1.82 mmol). The resulting dark brown solution was stirred for two hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 100 mL), and brine washed (3 X 300 mL). The resulting organic extract was separated, Na₂SO₄ dried, and concentrated. The resulting dark residue was subjected to SiO₂ chromatography with ethyl

acetate/ hexanes (1:1) to furnish a light yellow solid (321 mg, 62 %). ^1H NMR (400 MHz, CDCl_3) δ 10.08 (s, 1H), 7.56-7.48 (m, 2H), 7.12 (app t, $J = 7.3$ Hz, 2H), 6.94 (app t, $J = 8.5$ Hz, 1H), 6.88 (app t, $J = 8.7$ Hz, 1H), 5.33 (s, 2H), 2.45 (s, 3H); LC/MS C-18 column, $t_r = 2.94$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 470 (M+H). ES-HRMS m/z 469.9996 (M+H calcd for $\text{C}_{20}\text{H}_{13}\text{BrF}_4\text{NO}_3$ requires 470.0009).

10 Example 565



5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime

15

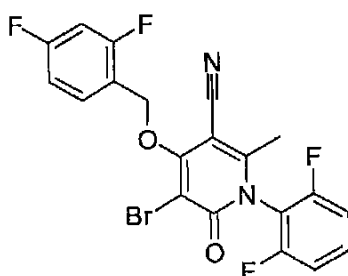
Step 1: To a room temperature solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde (316.5 mg, 0.673 mmol) in methanol (10.0 mL) was added solid $\text{NH}_2\text{OH}\cdot\text{H}_2\text{O}$ (300.0 mg, 4.32 mmol) and sodium acetate (480.0 mg, 5.85 mmol). The resulting suspension was stirred for 1.5 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then concentrated in vacuo and the resulting residue was diluted with methylene chloride (300 mL) and water washed (2 X 100 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated to furnish a light yellow solid (390 mg, 99 %). ^1H NMR (400 MHz, d_4 -MeOH with CDCl_3) δ 8.06 (s, 1H), 7.51-7.40 (m, 2H), 7.06 (app dd, J

20

25

= 8.6, 7.4 Hz, 2H), 6.88 (app dt, J = 8.3, 2.4 Hz, 1H), 6.83 (app dt, J = 9.2, 2.4 Hz, 1H), 5.13 (s, 2H), 2.76 (s, 3H); LC/MS C-18 column, t_r = 2.61 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection
 5 254 nm, at 50°C). ES-MS m/z 485 (M+H). ES-HRMS m/z 485.0093 (M+H calcd for $C_{20}H_{14}BrF_4N_2O_3$ requires 485.0118).

Example 566



10

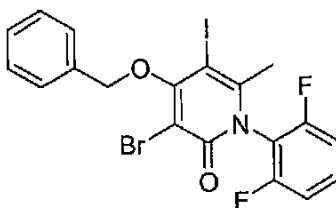
5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile

15 Step 1: To a room temperature solution of 5-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbaldehyde oxime (340.0 mg, 0.701mmol) in methylene chloride (8.0 mL) was added solid 1,1' carbonyl diimidazole (290.0 mg, 1.79 mmol) and sodium acetate (480.0
 20 mg, 5.85 mmol). The resulting solution was stirred for 1.5 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then concentrated in vacuo and the resulting residue was directly applied to SiO_2 chromatography with ethyl acetate/hexanes (3:7) to furnish a
 25 white solid (262 mg, 90 %). 1H NMR (400 MHz, $CDCl_3$) δ 7.61 (app q, J = 7.4 Hz, 1H), 7.52 (app tt, J = 8.4, 6.3 Hz, 1H), 7.14 (app dd, J = 8.6, 7.4 Hz, 2H), 6.94 (app dt, J = 8.5, 2.5 Hz, 1H), 6.88 (app dt, J = 8.5, 2.4 Hz, 1H), 5.43 (s, 2H),

2.32 (s, 3H); LC/MS C-18 column, t_r = 2.95 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). IR (neat) 3111, 3067, 3032, 2914, 2840, 2215 (nitrile stretch), 1678, 1587, 1470 cm^{-1} ; ES-MS m/z 467 (M+H).

5 ES-HRMS m/z 467.0037 (M+H calcd for $\text{C}_{20}\text{H}_{12}\text{BrF}_4\text{N}_2\text{O}_2$ requires 467.0013).

Example 567

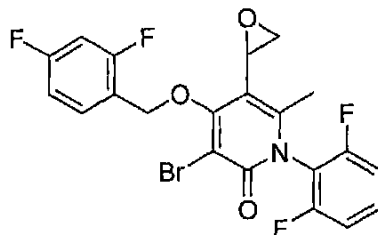


10 4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1: A solution of 4-(benzyloxy)-3-bromo-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (1.42 g, 3.50 mmol) in 1,2 dichloroethane (18 mL) was treated with solid N-iodosuccinimide (1.59 g, 7.06 mmol) and dichloroacetic acid (0.260 g, 2.01 mmol). The resulting solution was stirred and heated to 50 °C for 2.5 hours until complete consumption of starting material by LCMS. At this time the reaction was diluted with ethyl acetate (400 mL) and washed with sodium sulfite (5 % aqueous solution, 100 mL) and brine (3 X 200 mL). The resulting organic extracts were Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 30 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected and dried at 1 mm Hg vacuum to provide a solid (1.49 g, 82 %). ^1H NMR (400 MHz, CDCl_3) δ 7.62 (app d, J = 6.8 Hz, 2H), 7.51-7.38 (m, 4H), 7.09 (app t, J = 8.0 Hz, 2H), 5.20 (s, 2H), 2.39 (s, 3H); LC/MS C-18 column, t_r = 3.28 minutes (5 to 95% acetonitrile/water over 5

minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 532 (M+H). ES-HRMS m/z 531.9196 (M+H calcd for C₁₉H₁₄BrF₂INO₂ requires 531.9215).

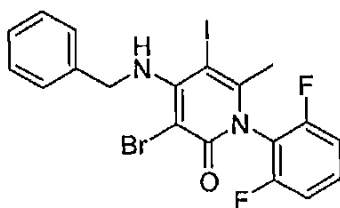
5 Example 568



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-oxiran-2-ylpyridin-2(1H)-one

10 Step 1: A sample of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-vinylpyridin-2(1H)-one (10.0 mg, 0.0214 mmol) was treated with a solution of dimethyl dioxirane in acetone (approx. 0.1 M, 5 mL, 0.5 mmol). The reaction vessel was capped and sealed, and the resulting
15 solution was stirred 6.0 hours. At this time the reaction was concentrated in vacuo and the resulting residue was subjected to SiO₂ chromatography with ethyl acetate/hexanes (4:6) to furnish a semi-solid (5.0 mg, 48 %). ¹H NMR (400 MHz, CDCl₃) δ 7.57 (app q, J = 7.4 Hz, 1H), 7.46 (app tt, J = 8.5, 6.2, 1H),
20 7.11 (app t, J = 8.0 Hz, 2H), 6.94 (app t, J = 8.2 Hz, 1H), 6.83 (app t, J = 9.2 Hz, 1H), 5.31 (AB-q, J = 10.9 Hz, Δ = 29.0 Hz, 2H), 3.63 (app t, J = 3.5 Hz, 1H), 3.03 (dd, J = 9.4, 5.0, 1H), 2.85 (dd, J = 5.2, 2.7, 1H), 2.14 (s, 3H); LC/MS C-18 column, t_r = 2.26 minutes (5 to 95% acetonitrile/water over 5
25 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 484 (M+H) and 502 (M+H₂O). ES-HRMS m/z 502.0273 (M+H₂O calcd for C₂₁H₁₇BrF₄NO₄ requires 502.0272).

Example 569

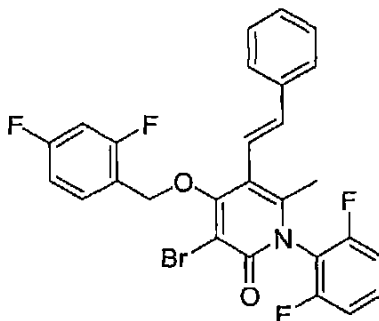


4-(benzylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-
 5 methylpyridin-2(1H)-one

Step 1: A slurry of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(
 (2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (80.0
 10 mg, 0.141 mmol) and benzyl amine (300 mg, 2.80 mmol) was
 heated to 63 °C and stirred for 1.0 hours until complete
 disappearance of starting material by LCMS analysis. The
 reaction mixture was then diluted with ethyl acetate (300 mL)
 and brine washed (3 X 200 mL). The resulting organic extracts
 15 were Na₂SO₄ dried, filtered, and concentrated in vacuo to a
 residue that was then subjected to SiO₂ chromatography with
 ethyl acetate/hexanes (3:7) to furnish a brown solid (60.0
 mg, 81 %). ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.22 (m, 6H), 7.04
 (app t, J = 8.4 Hz, 2H), 5.02 (br t, J = 1.6 Hz, 1H), 4.86
 20 (d, J = 5.5 Hz, 2H), 2.37 (s, 3H); LC/MS C-18 column, t_r = 3.02
 minutes (5 to 95% acetonitrile/water over 5 minutes at 1
 mL/min with detection 254 nm, at 50°C). ES-MS m/z 531 (M+H).
 ES-HRMS m/z 530.9344 (M+H calcd for C₁₉H₁₅BrF₂IN₂O requires
 530.9375).

25

Example 570



3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methyl-5-[(E)-2-phenylethenyl]pyridin-2(1H)-one

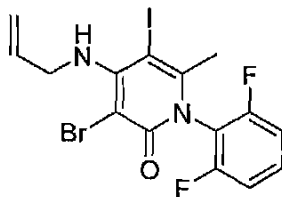
5

Step 1: To an anhydrous -78°C solution of β -bromostyrene (1.80 g, 10.0 mmol) in ether (18 mL) was added sequentially a solution of zinc chloride (10.0 mL, 1.0 M ether, 10.0 mmol) over 1.0 minute and a solution of tert-butyl lithium (15.0 mL, 1.6 M pentanes, 24.0 mmol) over 8.0 minutes. The resulting solution became cloudy and the reaction mixture was allowed to warm to room temperature on its own accord (over 30 minutes). After an additional 1.0 hour, the suspension was transferred by syringe directly to a separate vessel containing a solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.50 g, 2.64 mmol) and tetrakis(triphenylphosphine)palladium (294 mg, 0.254 mmol) in anhydrous THF (4 mL). This resulting suspension was heated to 55°C for 40 minutes and cooled to room temperature, whereby it was stirred under a positive pressure of argon for an additional 4.0 hours until complete disappearance of starting material by LCMS analysis. The reaction suspension was subsequently treated with NaHCO_3 and brine (100 and 200 mL, respectively). The resulting emulsion was extracted with ethyl acetate (3 X 300 mL) and the organic extracts were Na_2SO_4 dried, filtered, and concentrated in vacuo to a residue that was then subjected to SiO_2 chromatography with ethyl

acetate/hexanes (3:7) to furnish a reddish solid (1.25 g, 86 %). ^1H NMR (400 MHz, CDCl_3) δ 7.51-7.39 (m, 2H), 7.38-7.24 (m, 5H), 7.10 (app t, $J = 8.5$ Hz, 2H), 6.84 (d, $J = 17.2$ Hz, 1H), 6.82-6.75 (m, 1H), 6.74-6.68 (m, 1H), 6.69 (d, $J = 17.2$, 1H), 5.11 (br s, 2H), 2.15 (s, 3H); LC/MS C-18 column, $t_r = 3.74$ minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 544 ($M+H$). ES-HRMS m/z 544.0565 ($M+H$ calcd for $\text{C}_{27}\text{H}_{19}\text{BrF}_4\text{NO}_2$ requires 544.0530).

10

Example 574



15

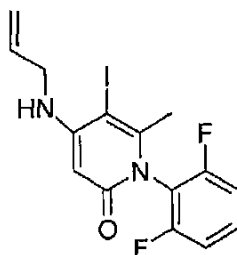
4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

Step 1: A slurry of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.40 g, 2.46 mmol) and allyl amine (1.98 mg, 34.6 mmol) was heated to 50 °C and stirred for 1.0 hours until complete disappearance of starting material by LCMS analysis. The reaction mixture was then concentrated in vacuo (1.0 mm Hg) for 2 days at 50 °C to furnish a brown solid (1.18 g, 99 %). ^1H NMR (300 MHz, CDCl_3) δ 7.43 (app tt, $J = 8.4, 6.2$, 1H), 7.09 (app t, $J = 8.4$ Hz, 2H), 6.02 (app dq, $J = 11.0, 6.2$ Hz, 1H), 5.39 (dd, $J = 16.9, 1.8$ Hz, 1H), 5.30 (dd, $J = 11.0, 1.8$ Hz, 1H), 4.84 (br s, 1H), 4.35 (br s, 2H), 2.42 (s, 3H); LC/MS C-18 column, $t_r =$

2.71 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 481 (M+H). ES-HRMS m/z 480.9261 (M+H calcd for C₁₅H₁₃BrF₂IN₂O requires 480.9219).

5

Example 575



4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

10

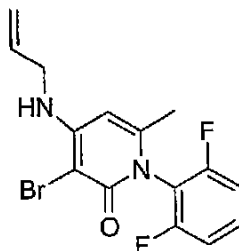
Step 1: A solution of 4-(allylamino)-3-bromo-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one (1.00 g, 2.07 mmol) and tetrakis(triphenylphosphine)palladium (420 mg, 0.363 mmol) in anhydrous THF (10 mL) under an argon stream was heated to 64 °C and stirred for 12 hours until complete disappearance of starting material by LCMS analysis. The reaction suspension was subsequently treated with brine (600 mL). The resulting emulsion was extracted with ethyl acetate (3 X 400 mL) and the organic extracts were anhy. Na₂SO₄ dried, filtered, and concentrated in vacuo to a residue that was then subjected to SiO₂ chromatography with ethyl acetate/hexanes (gradient 3:7) to furnish a solid (376 mg, 45 %). ¹H NMR (400 MHz, d₄-MeOH) δ 7.55 (app tt, J = 8.7, 6.3, 1H), 7.18 (app t, J = 7.6 Hz, 2H), 5.89 (app ddd, J = 15.4, 10.3, 5.1 Hz, 1H), 5.01 (app d, J = 17.0, Hz, 1H), 5.50 (s, 1H), 5.22 (app d, J = 11.0 Hz, 1H), 4.35 (app d, J = 5.0 Hz, 2H), 2.36 (s, 3H); LC/MS C-18 column, t_r = 2.33 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection

25

254 nm, at 50°C). ES-MS m/z 403 (M+H). ES-HRMS m/z 403.0133 (M+H calcd for C₁₅H₁₄F₂IN₂O requires 403.0113).

Example 576

5



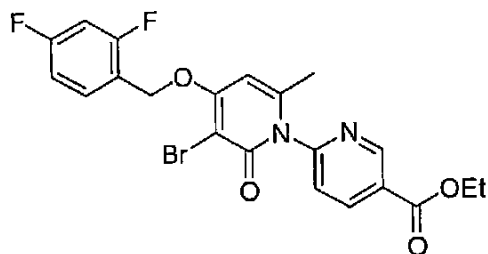
4-(allylamino)-1-(2,6-difluorophenyl)-5-iodo-6-methylpyridin-2(1H)-one

10

Step 1: A solution of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one (197 mg, 0.445 mmol) and allyl amine (1.32 mg, 23.1 mmol) in THF (6.0 mL) was heated to 68 °C and stirred for 74.0 hours. The reaction mixture was then concentrated in vacuo (30 mm Hg) to furnish a residue that was subjected to SiO₂ chromatography with ethyl acetate/hexanes (3:7) to furnish a solid (36.0 mg, 23 %). ¹H NMR (400 MHz, d₄-MeOH) δ 7.55 (app tt, J = 8.5, 6.5, 1H), 7.18 (app t, J = 8.5 Hz, 2H), 6.14 (s, 1H), 5.91 (app dq, J = 11.5, 6.4 Hz, 1H), 5.23 (dd, J = 17.0, 1.5 Hz, 1H), 5.19 (dd, J = 11.0, 1.6 Hz, 1H), 4.00 (app d, J = 4.7 Hz, 2H), 1.98 (s, 3H); LC/MS C-18 column, t_r = 2.24 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 355 (M+H). ES-HRMS m/z 355.0257 (M+H calcd for C₁₅H₁₄F₂BrF₂N₂O requires 355.0252).

25

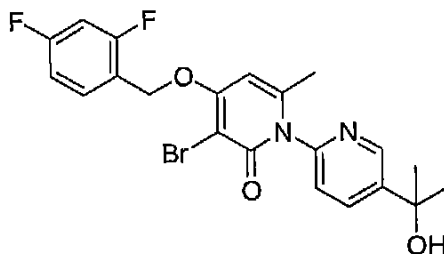
Example 577



ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2H-1,2'-bipyridine-5'-carboxylate

5 Step 1: To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (500.0 mg, 1.51 mmol) and Cs_2CO_3 (1.50 g, 4.60 mmol) in 1-methyl-2-pyrrolidinone (3.0 mL) was added ethyl 6-chloronicotinate (900 mg, 4.85 mmol). The resulting suspension was stirred and heated to 106
10 °C for 36 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2
15 chromatography with ethyl acetate/hexanes (3:7) to furnish a solid. ^1H NMR (400 MHz, d_4 -MeOH) δ 8.68 (app d, J = 2.5 Hz, 1H), 8.39 (dd, J = 8.7, 2.3 Hz, 1H), 7.62 (app q, J = 8.2 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.08 (s, 1H), 7.08-6.99 (m, 2H), 5.31 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H),
20 1.37 (t, J = 7.1 Hz, 3H); LC/MS C-18 column, t_r = 3.44 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 479 ($M+H$). ES-HRMS m/z 479.0401 ($M+H$ calcd for $\text{C}_{21}\text{H}_{18}\text{BrF}_2\text{N}_2\text{O}_4$ requires 479.0431).

25 Example 578

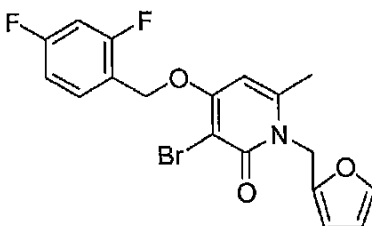


3-bromo-4-[(2,4-difluorobenzyl)oxy]-5'-(1-hydroxy-1-methylethyl)-6-methyl-2H-1,2'-bipyridin-2-one

5 Step 1: To a 0 °C solution of methyl magnesium bromide (3.0 M, 3.5 mL, 10.5 mmol) was added dropwise over 15 minutes a solution of ethyl 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxo-2H-1,2'-bipyridine-5'-carboxylate (500.0 mg, 1.05 mmol) in THF (4.0 mL). The internal temperature of the
10 reaction was never allowed to exceed 0 °C. The resulting solution was maintained for 30 minutes until complete consumption of starting material by LCMS analysis. Next, a solution of ammonium chloride (saturated aqueous, 160 mL) was added. The reaction mixture was extracted with ethyl acetate
15 (3 X 100 mL) and the resulting organic extracts were separated, Na₂SO₄ dried, and concentrated in vacuo to a residue that was subjected to SiO₂ chromatography with ethyl acetate/hexanes (gradient 3:7 to 6:4) to furnish a solid (386 mg, 79 %). ¹H NMR (400 MHz, d₄-MeOH) δ 8.23 (app d, J = 2.8
20 Hz, 1H), 7.97 (dd, J = 8.6, 2.3 Hz, 1H), 7.61 (app q, J = 8.2 Hz, 1H), 7.06-7.00 (m, 3H), 7.00 (s, 1H), 5.30 (s, 2H), 2.38 (s, 3H), 1.54 (s, 6H); LC/MS C-18 column, t_r = 2.75 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 465 (M+H). ES-HRMS
25 m/z 465.0615 (M+H calcd for C₂₁H₂₀BrF₂N₂O₃ requires 465.0620). IR(neat) 3366, 3030, 2974, 1600, 1507, 1362, 1232 cm⁻¹. ¹³C NMR (400 MHz, d₄-MeOH, visible peaks with carbon fluorine coupling present) δ 164.4, 160.7, 158.9, 157.6, 143.6, 141.6, 137.5,

131.61, 131.56, 131.51, 131.46, 119.29, 119.25, 119.15,
119.11, 112.23, 111.55, 111.52, 111.33, 111.29, 106.0, 103.9,
103.7, 103.4, 96.8, 70.3, 64.9, 64.8, 30.5, 22.6.

5 Example 579

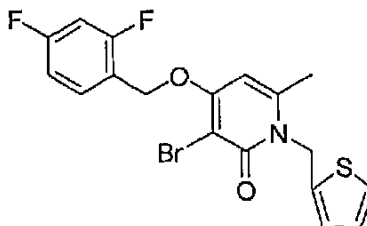


10 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2-furylmethyl)-6-
methypyridin-2(1H)-one

Step 1: Preparation of the title compound . To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (330.0 mg, 1.00 mmol) and NaH (48.0 mg, 2.0 mmol) in THF (3.0 mL) was added 2-(chloromethyl)furan (461 mg, 3.97 mmol). The resulting suspension was stirred and heated to 68 °C for 9 hours until complete consumption of starting material by LCMS analysis. The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL). The resulting organic extract was separated, Na₂SO₄ dried, and concentrated. The resulting dark residue was subjected to SiO₂ chromatography with ethyl acetate/hexanes (4:6) to furnish a solid. ¹H NMR (300 MHz, d₄-MeOH) δ 7.62 (app q, J = 8.4 Hz, 1H), 7.46 (s, 1H), 7.06 (app t, J = 8.7 Hz, 2H), 6.51 (s, 1H), 6.41-6.37 (m, 2H), 5.37 (s, 2H), 5.32 (s, 2H), 2.61 (s, 3H); LC/MS C-18 column, t_r = 2.63 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 410 (M+H).

ES-HRMS m/z 410.0177 (M+H calcd for $C_{18}H_{15}BrF_2NO_3$ requires 410.0198).

Example 580



5

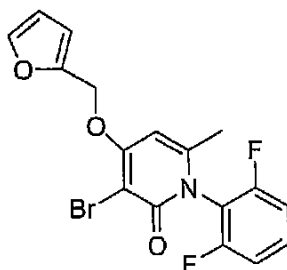
3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-1-(thien-2-ylmethyl)pyridin-2(1H)-one

Step 1: To a room temperature suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one (330.0 mg, 1.00 mmol) and NaH (48.0 mg, 2.0 mmol) in THF (3.0 mL) was added 2-(chloromethyl)thiophene (461 mg, 3.97 mmol). The resulting suspension was stirred and heated to 68 °C for 12 hours until complete consumption of starting material by LCMS analysis.

15 The reaction mixture was then diluted with ethyl acetate (400 mL), water washed (3 X 200 mL). The resulting organic extract was separated, Na_2SO_4 dried, and concentrated. The resulting dark residue was subjected to SiO_2 chromatography with ethyl acetate/hexanes (4:6) to furnish a solid. 1H NMR (400 MHz, d_4 -MeOH) δ 7.58 (app q, J = 8.2 Hz, 1H), 7.30 (app dd, J = 5.1, 1.2 Hz, 1H), 7.05 (d, J = 2.6 Hz, 1H), 7.01 (app t, J = 8.1 Hz, 2H), 6.93 (dd, J = 5.1, 3.4 Hz, 1H), 6.43 (s, 1H), 5.49 (s, 2H), 5.25 (s, 2H), 2.51 (s, 3H); LC/MS C-18 column, t_r = 2.74 minutes (5 to 95% acetonitrile/water over 5 minutes at 1

25 ml/min with detection 254 nm, at 50°C). ES-MS m/z 426 (M+H). ES-HRMS m/z 425.9936 (M+H calcd for $C_{18}H_{15}BrF_2NO_2S$ requires 425.9969).

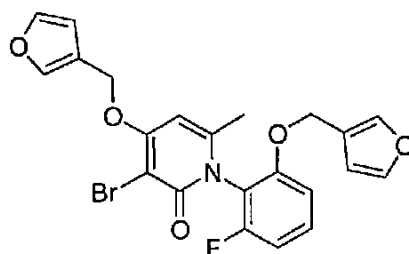
Example 581



3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-
 5 methylpyridin-2(1H)-one

Step 1: To a suspension of 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-
 2(1H)-one (250 mg, 0.445 mmol) and furfuryl alcohol (198 mg,
 10 2.0 mmol) in THF (2.5 mL) was added solid NaH (46.0 mg, 1.92
 mmol). Following the evolution of gas, the resulting
 suspension was heated to 60 °C and stirred for 3.5 hours until
 complete consumption of starting material by LCMS analysis.
 The reaction mixture was then diluted with ammonium chloride
 15 (saturated aqueous, 100 mL) and extracted with ethyl acetate
 (3 X 100 mL). The resulting organic extracts were separated,
 Na₂SO₄ dried, and concentrated to provide a residue that was
 subjected to SiO₂ chromatography with ethyl acetate/hexanes
 (3:7) to furnish a solid (110.0 mg, 49 %). ¹H NMR (400 MHz,
 20 d₄-MeOH) δ 7.63 (app tt, J = 8.5, 6.2, 1H), 7.62-7.61 (m, 1H),
 7.28 (app t, J = 8.5 Hz, 2H), 6.77 (s, 1H), 6.68 (d, J = 4.1
 Hz, 1H), 6.51(dd, J = 4.2, 3.9 Hz, 1H), 5.34 (s, 2H), 2.15 (s,
 3H); LC/MS C-18 column, t_r = 2.43 minutes (5 to 95%
 acetonitrile/water over 5 minutes at 1 ml/min with detection
 25 254 nm, at 50°C). ES-MS m/z 396 (M+H). ES-HRMS m/z 396.0044
 (M+H calcd for C₁₇H₁₃BrF₂NO₃ requires 396.0041).

Example 582



3-bromo-1-[2-fluoro-6-(3-furylmethoxy)phenyl]-4-(3-furylmethoxy)-6-methylpyridin-2(1H)-one

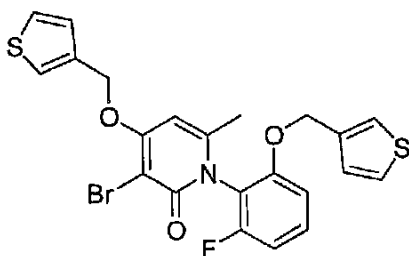
5

By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one (Example 581) and substituting 3-furylmethanol for furfuryl alcohol, the title compound was prepared in 55 % chemical

10 yield. ^1H NMR (400 MHz, $\text{d}_4\text{-MeOH}$) δ 7.64 (s, 1H), 7.55-7.42 (m, 3H), 7.40 (app t, $J = 1.4$ Hz, 1H), 7.12 (d, $J = 9.0$ Hz, 1H), 6.92 (app t, $J = 8.4$ Hz, 1H), 6.58 (s, 2H), 6.34 (br s, 1H), 5.21 (s, 2H), 5.03 (AB-q, $J = 14.0$ Hz, $\Delta = 58.0$ Hz, 2H), 1.99 (s, 3H); LC/MS C-18 column, $t_r = 2.67$ minutes (5 to 95%
15 acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 474 ($M+H$). ES-HRMS m/z 474.0346 ($M+H$ calcd for $\text{C}_{22}\text{H}_{18}\text{BrFNO}_5$ requires 474.0347).

Example 583

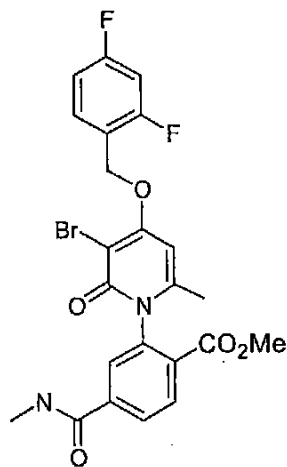
20



3-bromo-1-[2-fluoro-6-(thien-3-ylmethoxy)phenyl]-6-methyl-4-(thien-3-ylmethoxy)pyridin-2(1H)-one

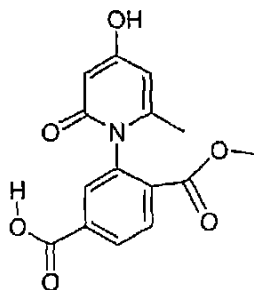
By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one Example 581 and substituting thien-3-ylmethanol for furfuryl alcohol, the title compound was prepared in 38 % chemical yield. ¹H NMR (400 MHz, d₄-MeOH) δ 7.50-7.42 (m, 3H), 7.33 (dd, J = 5.0, 3.0 Hz, 1H), 7.26 (br d, J = 2.0 Hz, 1H), 7.19 (dd, J = 5.0, 1.2 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 6.98 (dd, J = 14.9, 1.3 Hz, 1H), 6.93 (dt, J = 8.7, 1.0 Hz, 1H), 6.53 (br s, 1H), 5.33 (s, 2H), 5.14 (AB-q, J = 12.1 Hz, Δ = 50.0 Hz, 2H), 1.97 (s, 3H); LC/MS C-18 column, t_r = 2.93 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 506 (M+H). ES-HRMS m/z 505.9881 (M+H calcd for C₂₂H₁₈BrFNO₃S₂ requires 505.9890).

Example 584



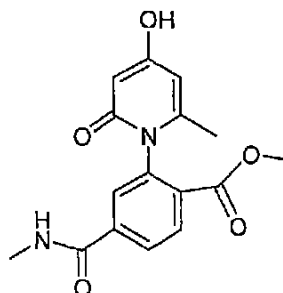
methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate

Step 1: Preparation of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid .



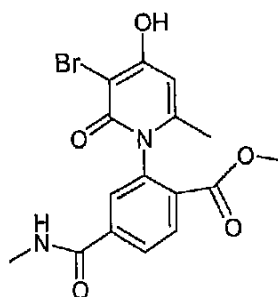
4-Hydroxy-6-methyl-2-pyrone (75.0 g, 595 mmol) and 3-amino-4-(methoxycarbonyl)benzoic acid (40.0 g, 0.205 mmol) were suspended in 56 ml of 1,2-dichlorobenzene in a 500 ml, 3-necked, round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 180 °C over a period of 26 minutes during which time all solids dissolved. Upon reaching an internal temperature of 180 °C, the reaction was allowed to maintain this temperature for an additional 25.0 minutes during which time the evolution of water from the reaction mixture was evident. Next, the heating apparatus was removed and the reaction was allowed to cool on its own accord to about 100 °C. The reaction was then diluted with 160 ml of toluene and stirred. After about 10 minutes, the reaction reached room temperature and a gummy solid had formed. The precipitate was filtered, washed with EtOAc (400 mL) and water (200 mL, 55 °C), and dried in vacuo to give a tan solid (30.5 g, 49%). ¹H NMR (400 MHz, d₄-MeOH) δ 8.20-8.09 (m, 2H), 7.84 (s, 1H), 6.08 (app d, J = 1.0 Hz, 1H), 5.76 (app d, J = 2.3 Hz, 1H), 3.76 (s, 3H), 1.91 (s, 3H). LC/MS, C-18 column, t_r = 1.96 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50 °C). ES-MS m/z 304 (M+H). ES-HRMS m/z 304.0803 (M+H calcd for C₁₅H₁₄NO₆ requires 304.0816).

Step 2: Preparation of methyl 2-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate .



To a solution of 3-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-(methoxycarbonyl)benzoic acid (from Step 1) (1.00 g, 3.30 mmol) in dimethylformamide (10 mL) and THF (10 mL) was added cyclohexylcarbodiimide-derivatized silica gel (a product of Silicycle chemical division Quebec, Canada) with a loading of 0.60 mmol/g (15.2 g, 9.73 mmol). After stirring for 30 minutes, a solution of methylamine (2.0 M, THF, 2.9 mL, 5.8 mmol) was added followed by the addition of 1-hydroxybenzotriazole (20.0 mg, 0.15 mmol). The reaction suspension was allowed to stir for 24 hours until the complete disappearance of starting material by LCMS analysis. The silica suspension was filtered and washed with 300 mL ethyl acetate/methanol (9:1) and 300 mL ethyl acetate/methanol (1:1). The resulting mother liquor was concentrated to furnish a brown semi-solid (898 mg, 86 %). ¹H NMR (300 MHz, d₄-MeOH) δ 8.22 (d, J = 8.0 Hz, 1H), 8.04 (dd, J = 8.3, 1.9 Hz, 1H), 7.73 (d, J = 1.6 Hz, 1H), 6.13 (d, J = 1.5, Hz, 1H), 5.80 (d, J = 2.2 Hz, 1H), 3.80 (s, 3H), 3.03 (s, 3H), 1.97 (s, 3H). LC/MS, C-18 column, t_r = 1.31 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 317 (M+H). ES-HRMS m/z 317.1142 (M+H calcd for C₁₆H₁₇N₂O₅ requires 317.1132).

Step 3: Preparation of methyl 2-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate .



To a room temperature suspension of methyl 2-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-

[(methylamino)carbonyl]benzoate (from Step 2) (406.0 mg,

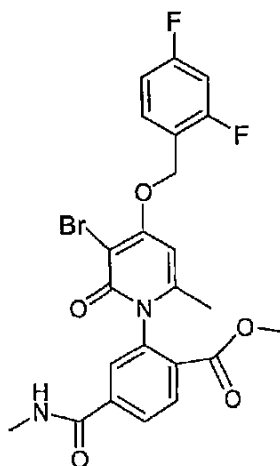
5 1.28 mmol) in CH_2Cl_2 (8 mL) was added solid N-bromosuccinimide (251 mg, 1.41 mmol) and stirred for 10 minutes until complete consumption of starting material by LCMS analysis. The reaction was next diluted with CH_2Cl_2 (5 mL), ethyl acetate (5 mL), and hexanes (1 mL). After approximately 30 minutes the

10 resulting white precipitate was filtered and washed with ethyl acetate (5 mL) to furnish a solid (298 mg, 62%). ^1H

NMR (400 MHz, d_4 -MeOH) δ 8.20 (d, $J = 8.2$ Hz, 1H), 8.01 (d, $J = 8.1$ Hz, 1H), 7.69 (s, 1H), 6.18 (s, 1H), 3.75 (s, 3H), 2.91 (s, 3H), 1.91 (s, 3H); LC/MS, $t_r = 1.27$ minutes (5 to 95%

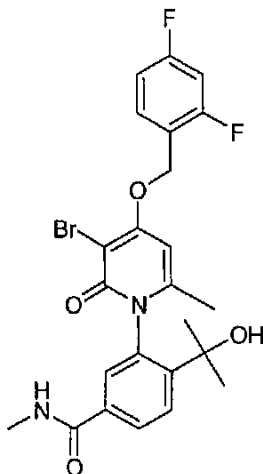
15 acetonitrile/water over 5 minutes at 1 mL/min with detection 254 nm, at 50°C). ES-MS m/z 395 ($M+H$). ES-HRMS m/z 395.0237 ($M+H$ calcd for $\text{C}_{16}\text{H}_{16}\text{BrN}_2\text{O}_5$ requires 395.0237).

Step 4: Preparation of the title compound .



To a solution of methyl 2-(3-bromo-4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)-4-[(methylamino)carbonyl]benzoate (from Step 3) (241 mg, 0.610 mmol) in dimethylformamide (0.5 mL) was added sequentially K_2CO_3 (240 mg, 1.73 mmol) and 2,4 difluorobenzyl bromide (0.085 mL, 0.66 mmol). The resulting suspension was stirred for 6.5 hours until complete consumption of starting material by LCMS analysis. The reaction was then diluted with ethyl acetate (200 mL) and brine washed (3 X 200 mL). The resulting organic extract was Na_2SO_4 dried, filtered, and concentrated in vacuo to approximately 5 mL volume. The resulting mother liquor rapidly precipitated and furnished an amorphous solid that was collected. 1H NMR (400 MHz, d_4 -MeOH) δ 8.22 (d, J = 8.2 Hz, 1H), 8.03 (dd, J = 8.2, 1.7 Hz, 1H), 7.71 (d, J = 1.8 Hz, 1H), 7.67 (app q, J = 8.3 Hz, 1H), 7.05 (app t, J = 8.6 Hz, 2H), 6.64 (s, 1H), 5.37 (s, 2H), 3.74 (s, 3H), 2.90 (s, 3H), 2.01 (s, 3H). LC/MS C-18 column, t_r = 2.87 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 mL/min with detection 254 nm, at 50°C). ES-MS m/z 521 ($M+H$). ES-HRMS m/z 521.0491 ($M+H$ calcd for $C_{23}H_{20}BrF_2N_2O_5$ requires 521.0518).

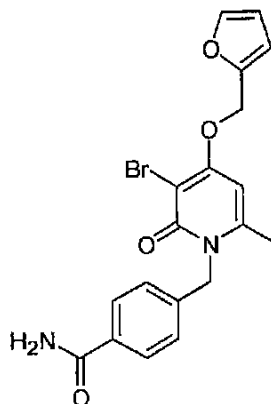
Example 585



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-(1-hydroxy-1-methylethyl)-N-methylbenzamide

Step 1: To a -10 °C solution of methyl magnesium bromide (3.0 M, 0.60 mL, 1.8 mmol) was added dropwise over 10 minutes a solution of methyl 2-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-[(methylamino)carbonyl]benzoate (85.0 mg, 0.163 mmol) in THF (1.0 mL). The internal temperature of the reaction was never allowed to exceed 0 °C. The resulting solution was maintained for 10 minutes. Next, a solution of ammonium chloride (saturated aqueous, 100 mL) was added. The reaction mixture was removed from the bath and resulting emulsion was extracted with ethyl acetate (3 X 100 mL) and the resulting organic extracts were separated, Na₂SO₄ dried, and concentrated in vacuo to a residue that was subjected to SiO₂ chromatography with ethyl acetate/hexanes (gradient 3:7 to 6:4) to furnish a solid (16 mg, 19 %). ¹H NMR (400 MHz, d₄-MeOH) δ 7.89 (d, J = 8.5 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.61 (app q, J = 8.2 Hz, 1H), 7.41 (s, 1H), 7.03-6.99 (m, 2H), 6.57 (s, 1H), 5.30 (s, 2H), 2.83 (s, 3H), 2.05 (s, 3H), 1.51 (s, 3H), 1.39 (s, 3H); LC/MS C-18 column, t_r = 2.28 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 521 (M+H). ES-HRMS m/z 521.0860 (M+H calcd for C₂₄H₂₄BrF₂N₂O₄ requires 521.0882).

Example 586

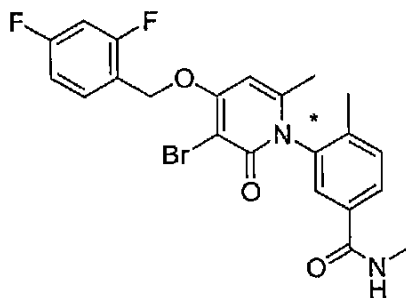


3-bromo-1-[2-fluoro-6-(thien-3-ylmethoxy)phenyl]-6-methyl-4-(thien-3-ylmethoxy)pyridin-2(1H)-one

5 By following the method of preparation of 3-bromo-1-(2,6-difluorophenyl)-4-(2-furylmethoxy)-6-methylpyridin-2(1H)-one Example 581 and substituting 4-{[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]methyl}benzamide for 3-bromo-4-[(2,4-difluorobenzyl)oxy]-1-(2,6-difluorophenyl)-6-methylpyridin-2(1H)-one, the title compound was prepared in 76 % chemical yield. ¹H NMR (400 MHz, d₄-MeOH) δ 7.83 (d, J = 8.1 Hz, 2H), 7.54 (app d, J = 1.1 Hz, 1H), 7.19 (d, J = 8.1 Hz, 2H), 6.57 (d, J = 3.2 Hz, 1H), 6.53 (s, 1H), 6.43 (dd, J = 3.1, 1.8 Hz, 1H), 5.45 (br s, 2H), 10 5.22 (s, 2H), 2.34 (s, 3H); LC/MS C-18 column, t_r = 1.98 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 417 (M+H). ES-HRMS m/z 417.0469 (M+H calcd for C₁₉H₁₈BrN₂O₄ requires 417.0444).

20

Example 587



(-)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

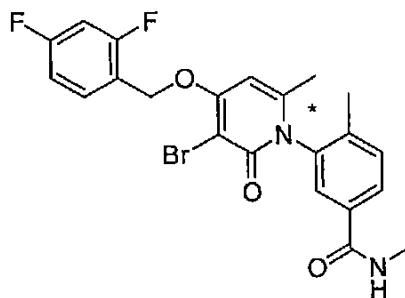
5

Example 489 (1.78 g, 4.36 mmol) were separated using a Chiral Technologies Chiralpak AD column (21 mm x 250 mm, 20 μ m) eluting with 100% ethanol (isocratic, 20 ml/min), loading 10 mg per injection. Fractions of the early-eluting atropisomer were pooled and concentrated in vacuo to the title compound (718 mg, 80%). Analytical chiral LC (Chiralpak AD, 4.6 mm x 50 mm, 10 μ m particle size, 0.5 ml/min ethanol) Retention time: 1.70 min, ee 94%. $[\alpha]_D = -23.8^\circ$ (5 mg/ml DMSO, 22 $^\circ$ C). ^1H NMR (400 MHz, DMSO- d_6) δ 8.42 (br qr, $J = 4.51$ Hz, 1H), 7.82 (dd, $J = 7.92, 1.70$ Hz, 1H), 7.68 (dt, $J = 8.24, 6.58$ Hz, 1H), 7.58 (d, $J = 1.59$ Hz, 1H), 7.48 (d, $J = 7.98$ Hz, 1H), 7.34 (dt, $J = 9.90, 2.50$ Hz, 1H), 7.18 (dt, $J = 8.53, 2.57$ Hz, 1H), 6.71 (s, 1H), 5.33 (s, 2H), 2.74 (s, 3H), 1.98 (s, 3H), 1.88 (s, 3H). ^{19}F -NMR (400 MHz, DMSO- d_6) δ -109.58 (quintet, $J = 7.49$ Hz, 1F), -113.65 (quartet, $J = 9.11$ Hz, 1F). ES-HRMS m/z 477.0612 ($M+H$ calcd for $\text{C}_{22}\text{H}_{20}\text{BrF}_2\text{N}_2\text{O}_3$ requires 477.0620).

15

20

Example 588



(+)-3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

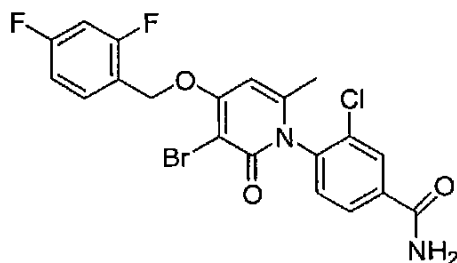
5

The title compound was prepared as in Example 587 , pooling the late-eluting atropisomer (722 mg, 81%).

Analytical chiral LC (Chiralpak AD, 4.6 mm x 50 mm, 10 μ m particle size, 0.5 ml/min ethanol) Retention time: 2.00 min,

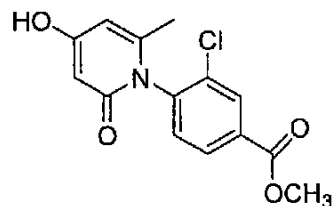
10 ee 98%. $[\alpha]_D^{25} = +28.2^\circ$ (5 mg/ml DMSO, 22 $^\circ$ C). ^1H NMR (400 MHz, DMSO- d_6) δ 8.42 (br qr, $J = 4.51$ Hz, 1H), 7.82 (dd, $J = 7.92$, 1.70 Hz, 1H), 7.68 (dt, $J = 8.24$, 6.58 Hz, 1H), 7.58 (d, $J = 1.59$ Hz, 1H), 7.48 (d, $J = 7.98$ Hz, 1H), 7.34 (dt, $J = 9.90$, 2.50 Hz, 1H), 7.18 (dt, $J = 8.53$, 2.57 Hz, 1H), 6.71 (s, 1H),
15 5.33 (s, 2H), 2.74 (s, 3H), 1.98 (s, 3H), 1.88 (s, 3H). ^{19}F -NMR (400 MHz, DMSO- d_6) δ -109.58 (quintet, $J = 7.49$ Hz, 1F), -113.65 (quartet, $J = 9.11$ Hz, 1F). ES-HRMS m/z 477.0614 ($M+H$ calcd for $\text{C}_{22}\text{H}_{20}\text{BrF}_2\text{N}_2\text{O}_3$ requires 477.0620).

20 Example 589



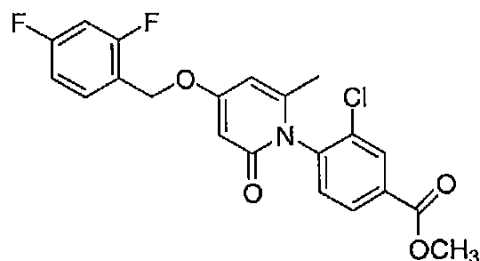
4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzamide

Step 1: Preparation of methyl 3-chloro-4-(4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate .



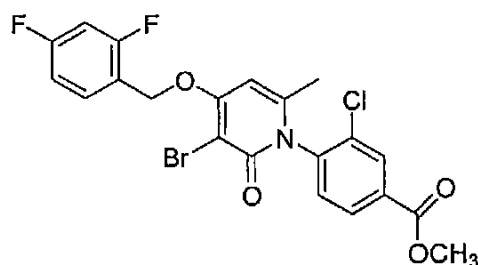
5 4-Hydroxy-6-methyl-2-pyrone (24.5 g, 193.9 mmol) and methyl-3-amino-2-chlorobenzoate (30 g, 161.6 mmol) were suspended in 75 ml of 1,2-dichlorobenzene in a 250 ml, 3-necked round bottom flask equipped with a J-Kem temperature controller probe, a Dean-Stark trap, and a heating mantle. The reaction was heated to 175°C for 20 minutes, during which, water and some 1,2-dichlorobenzene was collected in the Dean-Stark trap. The reaction was allowed to cool to about 110°C. At this point, 200 ml of toluene was added. The toluene mixture was allowed to stir for 72 hours at room temperature. A precipitate was collected on a filter pad. The precipitate was filtered and washed 3 times with toluene, 3 times with 50°C. water to remove excess pyrone, and dried in vacuo to give a tan solid (13.0 g, 27% yield). ¹H NMR (300 MHz, CD₃OD) δ 8.26 (d, J = 1.81 Hz, 1H), 8.14 (dd, J = 8.26, 1.81 Hz, 1H), 7.54 (d, J = 8.26, Hz, 1H), 6.14 (dd, J = 2.42, 1.0 Hz, 1H), 5.83 (d, J = 2.42 1H), 4.00 (s, 3H), 1.96 (s, 3H); LC/MS, t_r = 1.81 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 (M+H).

25 Step 2: Preparation of methyl 3-chloro-4-[4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]benzoate .



Methyl 3-chloro-4-((4-hydroxy-6-methyl-2-oxopyridin-1(2H)-yl)benzoate (from Step 1) (2.4g, 8.17 mmol) was taken up in DMF (10 ml). 2,4-difluorobenzylbromide (1.05 ml, 8.17 mmol) and K_2CO_3 (1.13 g, 8.17 mmol) were added. The reaction stirred for 6 hours at room temperature. At this time, the reaction was poured into water (200 ml) and extracted with ethyl acetate. The ethyl acetate layer was dried over Na_2SO_4 , filtered, and the solvent removed in vacuo to give amber oil (2.62 g, 77% crude yield). LC/MS, t_r = 2.79 minutes (5 to 95% acetonitrile/water over 5 minutes at 1 ml/min with detection 254 nm, at 50°C). ES-MS m/z 294 ($M+H$).

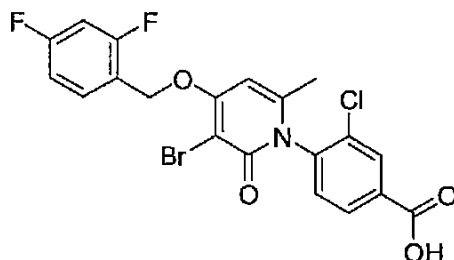
Step 3: Preparation of methyl 4-[3-bromo-4-((2,4-difluorobenzyl)oxy)-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate.



Methyl 3-chloro-4-[[4-((2,4-difluorobenzyl)oxy)-6-methyl-2-oxopyridin-1(2H)-yl]benzoate (from step 2) (2.60g, 6.21 mmol) was taken up in CH_2Cl_2 (20 ml). N-bromosuccinimide (1.11g, 6.21 mmol) was added and the mixture stirred at room temperature for 4 hours. The CH_2Cl_2 is removed in vacuo and

the residue is taken up in CH₃CN. The resulting precipitate is collected on a filter pad and washed with CH₃CN to yield a white solid (0.75 g, 24%). ¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, J = 1.88 Hz, 1H), 8.06 (dd, J = 8.19, 1.75 Hz, 1H), 7.59 (app q, J = 8.46 Hz, 1H), 7.33 (d, J = 8.19, 1H), 6.96 (dt, J = 8.06, 1.21 Hz, 1H), 6.89 - 6.84 (m, 1H), 6.13 (s, 1H), 5.26 (s, 2H), 3.95 (s, 3H), 1.95 (s, 3H); ES-MS m/z 478 (M+H). ES-HRMS m/z 497.9892 (M+H calcd for C₂₂H₁₆BrClF₂NO₄ requires 497.9914).

Step 4: Preparation of 4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoic acid.

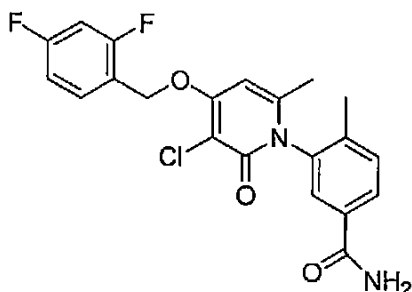


Methyl-4-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoate (2.30g, 4.61 mmol) was taken up in THF (20 ml) and H₂O (4 ml). 2.5 N NaOH (9.2 ml) was added to the vessel and the reaction stirred overnight to completion. Concentrated HCl was added dropwise until reaction was made acidic (pH = 1). H₂O (100 ml) and THF (100 ml) were added to the mixture. The contents were poured into a separatory funnel and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, the solvent removed in vacuo, and the residue was taken up in a 50% mixture of ethyl acetate/hexane. The precipitate was collected on a filter pad to yield a white powder (1.5g, 67%). ¹H NMR (300 MHz, DMSO) δ 13.59 (1H), 8.16 (d, J = 1.81 Hz, 1H),

8.06 (dd, $J = 6.24, 1.81$ Hz, 1H), 7.73 (app q, $J = 8.46$, 1H),
7.68 (d, $J = 8.26$ Hz, 1H), 7.38 (dt, $J = 9.48, 2.62$ Hz, 1H)
7.26 - 7.18 (m, 1H), 6.80 (s, 1H), 5.39 (s, 2H), 3.93 (s, 3H),
1.96 (s, 3H); ES-MS m/z 483 (M+H). ES-HRMS m/z 483.9749 (M+H
5 calcd for $C_{20}H_{14}BrClF_2NO_4$ requires 483.9757).

Step 5: 4-[3-Bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-3-chlorobenzoic acid (0.5 g, 1.03 mmol) was taken up in THF (10 ml). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0.22 g, 1.24 mmol) and N-methyl morpholine (0.34 ml, 3.09 mmol) were added. The mixture stirred at room temperature for 1 hour. At this time, NH_4OH (2.5 ml) was added and the reaction stirred at room temperature for one more hour. To the reaction mixture was added more THF (50 ml) and
15 water (200 ml). The mixture was extracted with ethyl acetate. The ethyl acetate extraction was washed with saturated brine solution. The brine layer was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The residue was taken up
20 in ethyl acetate and the resulting precipitate was collected on a filter pad to yield a white powder (0.38 g, 76%) 1H NMR (300 MHz, CD_3OD) δ 8.18 (d, $J = 1.81$ Hz, 1H), 8.02 (dd, $J = 8.26, 2.01$ Hz, 1H), 7.69 (app q, $J = 8.26$ Hz, 1H), 7.55 (d, $J = 8.06$ Hz, 1 H) 7.12 - 7.06 (m, 2H), 6.71 (s, 1H), 5.40 (s, 2H), 2.07 (s, 3H). ES-MS m/z 482 (M+H). ES-HRMS m/z 482.9919
25 (M+H calcd for $C_{20}H_{15}BrClF_2N_2O_3$ requires 482.9917).

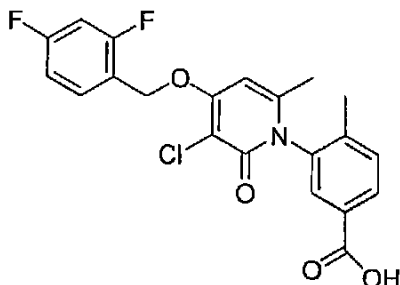
Example 590



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzamide

5

Step1: Preparation of 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid .



10

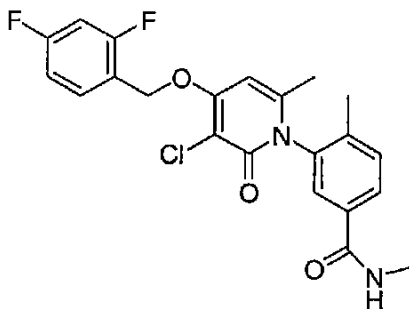
3-[4-[(2,4-Difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from above) (7.5g, 19.4 mmol) and NCS (2.6 g, 19.4 mmol) were taken up in 65°C dichloroethane (100 ml). A catalytic amount of dichloroacetic acid (2 drops) was added. After two hours the solvent was removed in vacuo and the residue was taken up in diethyl ether. The precipitate was collected on a filter pad and then taken up in 50% ethyl acetate/hexanes to remove residual succinimide. The precipitate was collected on a filter pad and then dried in vacuo to produce a white powder (4.2 g, 52%). ¹H NMR (300 MHz, CD₃OD) δ 8.10 (dd, J = 7.85, 1.81 Hz, 1H), 7.83 (d, J = 8.26, 1.81 Hz, 1H), 7.40 (app q, J = 8.26 Hz, 1H), 7.58 (d, J = 7.85 Hz, 1H), 7.13 - 7.06 (m, 2H), 6.74 (s, 1H), 5.40 (s, 2H), 2.14

20

(s, 3H), 2.04 (s, 3H); ES-MS m/z 420 (M+H). ES-HRMS m/z 420.0786 (M+H calcd for $C_{21}H_{17}ClF_2NO_4$ requires 420.0809).

Step 2: 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (1.5g, 3.57 mmol) was taken up in THF (30 ml). 2-Chloro-4,6-dimethoxy-1,3,5-triazine (0.75 g, 4.28 mmol) and N-methyl morpholine (1.18 ml, 10.72 mmol) were added. The mixture stirred at room temperature for 1 hour. At this time, NH_4OH (7.5 ml) was added and the reaction stirred at room temperature for one more hour. To the reaction mixture was added more THF (100 ml) and water (150 ml). The mixture was extracted with ethyl acetate. The ethyl acetate extraction was washed with saturated brine solution. The brine layer was extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. The residue was taken up in ethyl acetate and the resulting precipitate was collected on a filter pad to yield a white powder (1.32 g, 88%) 1H NMR (300 MHz, CD_3OD) δ 7.96 (dd, J = 7.85, 1.81 Hz, 1H), 7.71 (d, J = 1.81 Hz, 1H), 7.67 (app q, J = 8.06 Hz, 1H), 7.56 (d, J = 8.06 Hz, 1H), 7.12 - 7.06 (m, 2H), 6.74 (s, 1H), 5.40 (s, 2H), 2.13 (s, 3H) 2.05 (s, 3H). ES-MS m/z 419 (M+H). ES-HRMS m/z 419.0979 (M+H calcd for $C_{21}H_{18}ClF_2N_2O_3$ requires 419.0969).

Example 591



3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-N,4-dimethylbenzamide

5

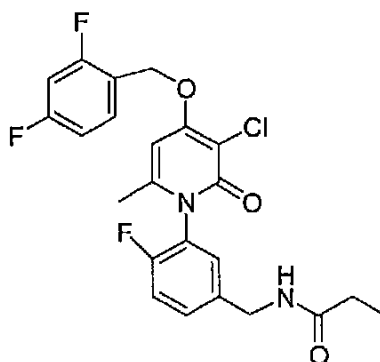
The title compound was prepared from 3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-methylbenzoic acid (from step 1 above) (1.5 g, 3.57 mmol) in dichloromethane (35 ml). To this mixture, 2.0 M methyl amine in THF (3.6 ml, 7.14 mmol) was added, followed, in order, by EDCI (0.67 g, 4.28 mmol), 1-hydroxybenzotriazole (0.58 g, 4.28 mmol) and triethylamine (0.99 ml, 7.14 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl and extracted 3 times with ethyl acetate.

15 The combined organic layer was then washed with saturated NaHCO_3 (aq.) and extracted 3 times with ethyl acetate. The organic layers were combined and washed with H_2O and extracted 3 times with ethyl acetate. The organic layers were combined and dried over Na_2SO_4 and evaporated. The resulting residue

20 was triturated with diethyl ether/hexane to obtain a solid, which was dried in vacuo to give a white solid (1.5g, 72%). ^1H NMR (300 MHz, CD_3OD) δ 7.90 (dd, $J = 8.06, 1.81$ Hz, 1H), 7.67 (app q, $J = 6.44$ Hz, 1H), 7.55 (d, $J = 8.06$ Hz, 1H), 7.13 - 7.06 (m, 2H), 6.74 (s, 1H), 5.40 (s, 2H), 2.93 (s, 3H), 2.13 (s, 3H), 2.04 (s, 3H); ES-MS m/z 433 ($\text{M}+\text{H}$). ES-HRMS m/z 433.1153 ($\text{M}+\text{H}$ calcd for $\text{C}_{22}\text{H}_{20}\text{ClF}_2\text{N}_2\text{O}_3$ requires 433.1125).

25

Example 592



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}propanamide

5

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0.56 mmol),

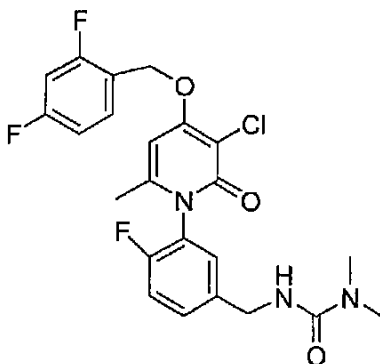
10 propionyl chloride (49 μ L, 0.56 mmol), triethylamine (195 μ L, 1.4 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. The reaction mixture was poured into a saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with ethyl acetate. The

15 organic phase was dried with Na_2SO_4 and concentrated in vacuo to obtain (240 mg, 91%) as a yellow solid. ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{SO}$) δ 8.3 (t, J = 5.8 Hz, 1H), 7.6 (q, J = 8.7 and 6.58 Hz, 1H), 7.38 (d, J = 7.78 Hz, 1H), 7.3 (dd, J = 2.6 and 7.6 Hz, 1H), 7.22 (d, J = 7.51 Hz, 1H), 7.12 (td, J = 2.0 and 6.5

20 Hz, 1H), 6.65 (s, 1H), 5.3 (s, 2H), 4.23 (d, J = 3.6 Hz, 2H), 2.1 (q, J = 7.7 Hz 2H), 1.98 (s, 3H), 0.98 (t, J = 7.5 Hz, 3H) ppm. ES-HRMS m/z 465.1203 ($M+H$ calcd for $\text{C}_{23}\text{H}_{21}\text{ClF}_3\text{N}_2\text{O}_3$ requires 465.1187).

25

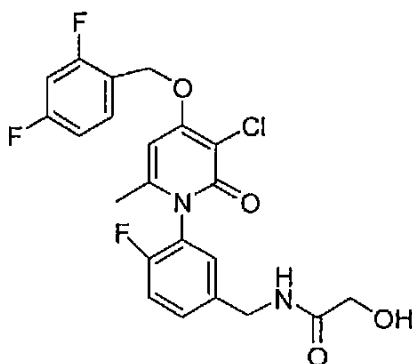
Example 593



N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl} dimethylurea

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0.56 mmol), dimethylcarbamy l chloride (52 μ L, 0.56 mmol), triethylamine (195 μ L, 1.4 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. The reaction mixture was poured into a saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with ethyl acetate. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to obtain the desired product (245 mg, 86%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 7.61 (q, J = 7.9 and 6.7 Hz, 1H), 7.4 (m, 1H), 7.3 (d, J = 9.3 Hz, 1H), 7.21 (m, 1H), 7.1 (m, 2H), 6.65 (s, 1H), 5.35 (s, 2H), 4.38 (s, 2H), 2.9 (s, 6H), 2.1 (s, 3H) ppm. ES-HRMS m/z 480.1269 ($M+H$ calcd for $\text{C}_{23}\text{H}_{22}\text{ClF}_3\text{N}_3\text{O}_3$ requires 480.1296).

Example 594

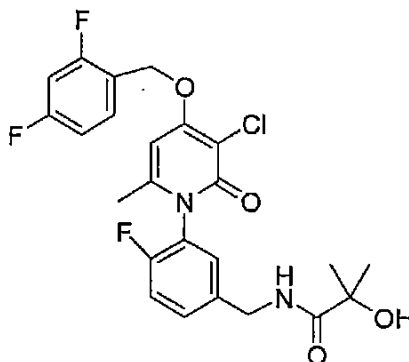


N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}-2-hydroxyacetamide

5

A 10 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-[(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one hydrochloride (250 mg, 0.56 mmol),
 10 acetoxyacetyl chloride (66 μ L, 0.62 mmol), triethylamine (195 μ L, 1.4 mmol) and tetrahydrofuran (4.0 mL). After stirring at 25° C for 5 min the reaction was completed by LC-MS. NaOH (2.5M, 2.24 mmol, 1.0 mL) and MeOH (2.0mL) was added and stirred for 10 min to give the title compound. The reaction
 15 mixture was acidified with concentrated HCl and extracted with ethyl. The organic phase was dried with Na₂SO₄ and concentrated in vacuo to obtain (217 mg, 78%) of the desired product as a yellow solid. ¹H NMR (400 MHz, (CD₃OD) δ 7.6 (q, J = 7.6 and 6.9 Hz, 1H), 7.44 (m, 1H), 7.34 (m, 2H), 7.22 (m, 2H), 6.63 (s, 1H), 5.35 (s, 2H), 4.41 (s, 2H), 4.0 (s, 2H),
 20 2.05 (s, 3H) ppm. ES-HRMS m/z 467.0957 (M+H calcd for C₂₂H₁₉ClF₃N₂O₄ requires 467.0980).

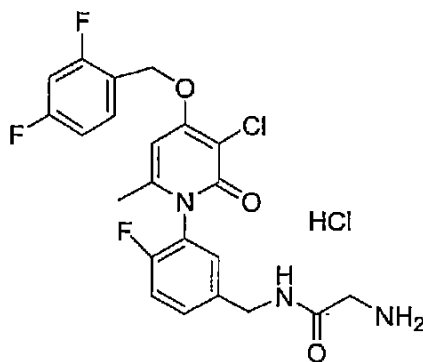
Example 595



- 5 N-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}-2-hydroxy-2-methylpropanamide

The title compound was prepared essentially as described in
 10 Example 594, with 1-chlorocarbonyl-1-methylethyl acetate substituting acetoxyacetyl chloride ^1H NMR (400 MHz, CDCl_3) δ 9.9 (q, $J = 8.2$ and 6.5 Hz, 1H), 9.7 (t, $J = 2.6$ Hz, 1H), 9.5 (t, $J = 8.9$ Hz, 2H), 9.3 (m, 1H), 9.2 (m, 1H), 8.6 (s, 1H) 7.6 (s, 2H), 6.8 (d, $J = 15$ Hz, 1H), 6.63 (d, $J = 15$ Hz, 1H), 4.42
 15 (d, $J = 3.2$ Hz, 6H), 3.99 (s, 3H) ppm. ES-HRMS m/z 495.1271 (M+H calcd for $\text{C}_{24}\text{H}_{23}\text{ClF}_3\text{N}_2\text{O}_4$ requires 495.1293).

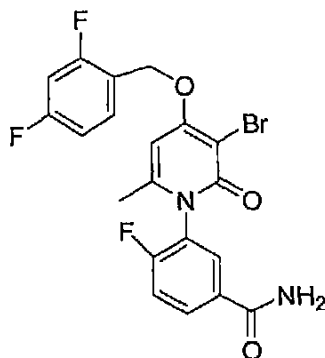
Example 596



N¹-{3-[3-chloro-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzyl}glycinamide hydrochloride

A 25 mL round bottomed flask equipped with stirbar and
 5 nitrogen inlet was charged with boc-glycine (105 mg, 0.6 mmol)
 and 8 mL of DMF. The mixture was cooled to 0° C and
 isboutylchloroformate (77.5 µL, 0.6 mmol) was added and stirred
 for 20 min. 1-[5-(aminomethyl)-2-fluorophenyl]-3-chloro-4-
 [(2,4 difluorobenzyl)oxy]-6-methylpyridin-2(1H)-one
 10 hydrochloride (250 mg, 0.6 mmol) was added and stirred for 3h.
 After completion of the reaction by LC-MS, concentrated HCl (2
 mL) and 2 mL of methanol was added to remove the boc group.
 The reaction was stirred for 24 h, neutralized with 2M NaOH
 and extracted with ethyl acetate. The organic phase was dried
 15 with Na₂SO₄ and concentrated in vacuo to obtain (196 mg, 66%)
 of the desired product as a the HCl salt. ¹H NMR (400 MHz,
 (CD₃OD) δ 7.6 (q, J = 8 and 6.5 Hz, 1H), 7.5 (m, 1H), 7.3 (m,
 2H), 7.0 (m, 2H), 6.63 (s, 1H), 5.35 (s, 2H), 4.4 (q, J = 15
 and 13.6 Hz, 2H), 3.7 (s, 2H), 2.05 (s, 3H) ppm. ES-HRMS m/z
 20 466.1157 (M+H calcd for C₂₂H₂₀ClF₃N₃O₃ requires 466.1140).

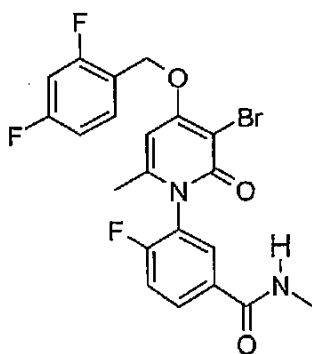
Example 597



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-
 25 1(2H)-yl]-4-fluorobenzamide

A 250 mL round bottomed flask equipped with stirbar and nitrogen inlet was charged with 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (3.65g, 7.8 mmol), 4-methylmorpholine (2.6 mL, 23.4 mmol), 2-chloro-4,6-dimethoxy-1,3,5-triazine (1.64g, 9.36 mmol) and tetrahydrofuran (40 mL). After stirring the mixture for 30 min at 25° C, NH₄OH (20.0 mL) was added. The mixture was stirred for 30 min and diluted with water. The product precipitated from solution. The precipitated was filtered and washed with water and diethyl ether to give the title compound (2.37g, 65%) as a white solid. ¹H NMR (400 MHz, (CD₃)₂SO) δ 7.9 (d, J = 7.3 Hz, 1H), 7.61 (q, J = 8.6 and 6.7 Hz, 1H), 7.5 (m, 2H), 7.3 (t, J = 9.6 Hz, 1H), 7.15 (t, J = 8.7 Hz, 1H), 6.7 (s, 1H), 5.36 (s, 2H), 2 (s, 3H) ppm. ES-
HRMS m/z 469.0172 (M+H calcd for C₂₀H₁₅BrF₃N₂O₃ requires 469.0195).

Example 598



3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluoro-N-methylbenzamide

A solution of 3-[3-bromo-4-[(2,4-difluorobenzyl)oxy]-6-methyl-2-oxopyridin-1(2H)-yl]-4-fluorobenzoic acid (1 g, 2.1 mmol) in N,N-dimethylformamide (20 mL) was cooled to -10 C. Isobutyl chloroformate (0.27 mL, 2.1 mmol) and N-methylmorpholine (0.23 mL, 2.1 mmol) were added to the reaction